OXFORD MEDICAL PUBLICATIONS

# CLINICAL PATHOLOGY IN PRACTICE

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## WITH A SHORT ACCOUNT OF VACCINE-THERAPY

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# PREFACE

THE aim of this book is to present the practitioner with a brief survey of the scope and usefulness of modern pathological methods as applied to the diagnosis and treatment of disease. It is not intended to serve as a laboratory textbook; indeed, some care has been exercised to exclude descriptions of technique with which the pathologist, and not the practitioner, is chiefly concerned. Nor does it profess to be a systematic account of pathology. Its object is to aid the practitioner in the choice of cases that will repay pathological examination, to indicate the materials that are necessary for the purpose, to describe the methods by which these materials are to be obtained, and to consider the interpretation that is to be put upon the results of the investigation.

The attempt to keep these practical objects in view has perhaps led to inequalities in the treatment of the different sections. Thus, in some chapters the diseases met with form the subject of the discussion, whereas in others it is the materials dealt with.

Nearly all the results considered in these pages have been verified by the author himself, or by his colleagues, in the course of investigations made upon

cases in which he has been interested clinically. When the results differ from those obtained by other observers this fact is taken into due consideration. No excuse is perhaps needed for the paucity of references to the literature of the subject.

Five of the chapters now printed have appeared elsewhere in somewhat different form; amongst these are the two chapters dealing with vaccine-therapy, in the writing of which the author has had the valued co-operation of his colleague Mr. Girling Ball. Thanks are also due to Dr. Mervyn Gordon and to Dr. James Hussey for several important suggestions made after reading the proof-sheets, and to Dr. A. E. Gow for assistance in compiling the Index.

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## INTRODUCTORY

I. The advances made in Medicine during the past twenty years have been due almost entirely to the introduction of special tools in the examination of the patient. The use of tools in diagnosis detracts nothing from the fundamental importance of examination conducted by the unaided senses. The physician who is tempted to substitute the microscope for a trained eye and an experienced hand stands to lose a good deal by the exchange. But to supplement the observations of the bedside by the investigations of the laboratory constitutes, in the matter of diagnosis, the whole duty of the medical man.

II. The special scrutiny of materials derived from the patient, as against the examination of the patient himself, is the study of Clinical Pathology. This branch of Medicine has of late years become very important, and its study has necessitated expert training on the part of the student. Such training has in most instances been carried out under lamentably defective conditions, and for it a totally inadequate period of time has been allotted in a curriculum already overcrowded by matters of far less urgency. Even to-day there is at many teaching centres but a meagre appreciation of the great value of sound instruction in clinical pathology.

So important, indeed, has this kind of work become that there is no little danger of the student concluding that it falls properly to the duty of the pathologist, whom

he regards in the light of a specialist in these matters. This very serious error receives support from the practice in vogue at some hospitals of putting the routine ward investigations in the hands of senior men in the pathological department. By these demonstrators of pathology reports are handed in to the physicians and surgeons; the clerks and dressers are meantime mostly ignorant, if not of the significance of the conclusions arrived at, yet ignorant of the practical steps by which these conclusions have been reached. Clerks and dressers should be encouraged and taught to undertake blood-counts and blood-cultures, agglutination tests, full urine examinations, and various other investigations which are of everyday service in the wards, in the same way that they are encouraged and taught to auscultate a heart or to palpate an abdomen. As these latter efforts are supervised by the physician and the surgeon with the assistance of their house officers, so should the former be supervised by the pathologist with the help of his demonstrators.

Prior to the period of clerking and dressing in the wards the fundamentals of clinical pathology should have been mastered by three months' clerking in the pathological laboratories. And to gain the necessary time for this very moderate outlay upon so vital a part of the doctor's training, some section of the earlier medical studies which has but a remote bearing upon practical medicine should be omitted or shortened. And it would not be difficult to find such a section. Indeed, the preparation for this important work might with great advantage begin earlier still. Thus the course of practical physiology might include a fuller histological study of normal blood and a closer acquaintance with such simple instruments as the Thoma-Zeiss pipette. The course of practical chemistry might cover

a detailed study of the constituents of normal urine, fæces, and the digestive juices.

III. Reference has been made to the danger of substituting the investigations of clinical pathology for the equally important physical examination of the patient. It certainly seems necessary to utter a warning against this tendency, which promises to become a stumbling-block not only to the student but also to the pathologist. Those physicians whose duty it is to examine students for their diploma meet with numerous instances of their reversal of the proper order of the facts relating to disease. One such instance will suffice. Asked what points in a case of pneumonia would lead to a diagnosis of empyema a student commenced his answer by saying, 'The presence of a leucocytosis.' A consulting physician who recently visited one of his old wards was told by the sister that things had changed very much since his days. 'A new patient,' she lamented, 'had his blood examined and an X-ray photograph taken, and then they left him!' Had she added that the blood-count was made by the research clerk, and the skiagram was taken by the radiographer, the physician would have got a better idea of the labours devolving upon the clinical clerk of the case. In all seriousness, a caution is necessary. The student should be warned against the glamour of the royal road. To change the physician for the pathologist can but end in disaster; but to add to sound clinical observations the findings of the microscope and the test-tube sums up all the notable advances made in Medicine since the days of Laennec.

IV. The cases of serious illness in which some sort of pathological investigation is not indicated are very few. But to choose the form of investigation which will be most useful in helping to establish the diagnosis and assist in

the treatment is not always easy. The proper choice often calls for the exercise of much clinical experience, together with a knowledge of what is possible on the part of the pathologist. It is not perhaps too much to say that the interpretation of the results of the investigation will be all the more valuable if the medical attendant fully understands the nature of the investigations undertaken. In regard to this question of the choice and the limitation of the particular research most likely to be of service, anomalies are not infrequently seen. It sometimes transpires that the pathological investigations undertaken in a difficult case outweigh both in number and in complexity the clinical observations. The practitioner is then like to be confused by a number of data the significance of which he cannot appreciate. And some of these data, obtained at no little expense to the patient, may have no sort of bearing upon the essential points of the case, or may carry with them no therapeutic indication. This state of things is not so often due to errors on the part of the pathologist as to mistakes in judgement on the part of the practitioner in charge of the patient.

V. Not only are care and knowledge required on the part of the medical attendant in order to choose the pathological investigation which promises most assistance in the diagnosis: accurate work, with a liberal training in the constant use of ' controls ', is necessary on the part of the pathologist. And more than this, the pathologist should be able to write a report which is kept well within the data at his command. This seems simple enough at first sight. But a glance through a number of clinical pathological reports reveals too often how easy it is to fall into the temptation of going beyond the facts. When this error is committed the practitioner may easily be led astray. Supported, as he thinks he is, by the bed-rock of pathological investigation, he answers his

patient's question in no uncertain voice,—to find, perhaps, that the bed-rock was in reality but a negation, and therefore worthless as a basis for a positive opinion. One example will suffice. 'REPORT on film specimen of urethral discharge. This material consists of degenerate muco-pus, in which are a small number of (skin) micrococci. The gonococcus is absent.' Here is an instance of a bad report. It should have read as follows: 'This material appears to consist of mucus with pus cells, the latter showing signs of degeneration. A few cocci are present, but these have no morphological or other resemblance to gonococci. Their source and nature cannot be ascertained from examination of the slide alone.' The assumption that the cocci are 'skin' cocci is wholly unwarranted from a film examination. And to convert 'no gonococci found' into 'gonococcus absent' is likely to lead to serious mischief.

VI. The report of the pathologist having been received, the clinician considers if he can by means of the added data complete a diagnosis which was only partial without them, or make a diagnosis where none was previously possible. If a full diagnosis has been made, this is now reviewed in the light of the new facts, and it is seen whether or no the diagnosis is confirmed. If the diagnosis be not confirmed the clinician does not forthwith reject it but considers first of all the value attaching to the particular investigations upon which the report is based. Especially does he consider what is the range of error in the performance of the investigation, and what may be the range of error in the interpretation of the result. In these matters he does well to inquire of the pathologist himself, whom it behoves to study this matter very carefully. For just as the clinician does well constantly to submit his conclusions to pathological proof or disproof, so the pathologist does well repeatedly to verify his findings

by the actual course of the disease as exemplified in the patient.

Given that proper controls are used, that the technique of the examination is not so delicately planned that it becomes too fine for practical use, and that the personal equation can be properly eliminated, it may be assumed that the range of error in the performance of the investigation is reduced to a minimum. But the interpretation of the result is a matter upon which views must never be held too rigidly. For even the pathologist must be prepared to modify his views of any investigation from time to time as his experience grows.

VII. Pathological reports fall into two classes as regards their significance. This may be *absolute* or it may be *relative*. (i) A report has an absolute significance if it records an isolated fact, such as the demonstration of a micro-organism of known pathogenic properties or of a tissue of recognized morbid histology. Thus the demonstration of the tubercle bacillus in a specimen of expectoration admits of only one interpretation: that somewhere in the respiratory system of the patient an ulcerating tuberculous focus exists. Again, if a lymphatic gland removed from the body reveals the structure of squamous-celled carcinoma, it is certain that the patient is suffering from a cancer in some organ whose lymphatics travel to that gland. These are facts and they admit of no argument.

(ii) But the report may have only a relative significance. This is the case when it refers to either of the various 'tests' which depend upon certain 'specific' antibodies existing in the blood or other body fluids: agglutinins, precipitins, &c. For, in the first place, it is universally agreed that the very specificity of these substances is a relative quantity. And, in the second place, entailing as they do fine quantitative

measurements, some arbitrary convention is adopted to bring these tests within the sphere of practical application. There is probably no such test which is universally true, be it positive or negative. Widal's reaction may at times be present in a disease which is not typhoid fever, and it may be absent in one that is. Any of the tuberculin tests may upon occasion be positive in a patient without active tuberculosis, and may be negative with it. There may be a high leucocytosis in appendicitis with no pus formation, and an acute abscess may form with very little rise in the count of white cells. And so on. Pathological 'tests' are to be used as confirmatory evidence, not as absolute guides.

The possible concurrence of a positive pathological test with an altogether independent disease-process must never be forgotten. A patient may give a positive Wassermann reaction, indicating previous infection by the virus of syphilis, yet the symptom-complex on account of which his blood or cerebro-spinal fluid has been tested may be due to an altogether different cause. A tuberculin test may be positive, not because the lesion which is being studied, and the nature of which is doubtful, is tuberculous, but because there is an active but quite hidden focus of tuberculosis elsewhere in the body. It may be quite legitimate to disregard the possibility of these fallacies after due consideration of all the facts of the case, but that the fallacies exist must never be forgotten.

VIII. The moral of very much of what has been said is that there are many cases of disease in which all-important information can be afforded by appropriate pathological investigations, but that there are pitfalls into which the unwary may easily stumble if judgement be not exercised with regard to these investigations and the interpretation of their results. Free intercourse between clinician and

pathologist, and due consideration for both aspects of the diagnostic problem, lead to the fewest blunders and the most helpful results. Either observer, working alone, is apt to be ignorant of the other's methods and powers, and is therefore prone to attach undue importance to his own sphere of activity. Ignorance leads to autocracy, autocracy leads to the making of claims which events do not justify, and unfulfilled claims cause the enemy to blaspheme. The whole truth will never be found at the bedside; still less will it be found in the laboratory; the hopes of Medicine lie in the close dependence of each field of observation upon the other.

## CHAPTER II

### THE COLLECTION OF PATHOLOGICAL MATERIAL, WITH SOME HINTS ON PORTABLE APPARATUS

REFERENCE has already been made to the great importance attaching to the examination of materials derived from the patient. And seeing that herein lies much of the *motif* of these pages a short section may not unreasonably be devoted to a general consideration of the collection and preservation of pathological materials.

Whilst commenting upon a supposed decadence in clinical methods, a physician was recently heard to remark that nowadays the young consultant needed a special van at the end of the train to carry his apparatus. In this remark lay more than a hint that there is a growing tendency for apparatus to take the place of brains. It will, however, be readily granted that although the use of tools may be very valuable in the investigation of disease, it still remains true that the more important of the two factors concerned in elucidating a difficult case is the man in the compartment in front, not the apparatus in the van behind. But there was also in the physician's remark a hint as to the cumbersome nature of the tools required for the investigations of clinical pathology. It must be allowed that the taunt is sometimes justified. There is a crudity about the arrangements of some workers in the matter of pipettes, syringes, culture tubes, &c., which leads to a multiplication of cases, flasks, wire cages, &c., and often suggests an absence of facility in the use of the contents of these receptacles.

It can be so arranged that all the essential articles required for the collection of materials at the bedside are carried in one case. Some years ago Messrs. Burroughs & Wellcome made for the writer an extremely neat and compact case, which was primarily intended for blood-culture and lumbar-puncture work. In both of these investigations, although it is possible to compromise in this matter (see p. 25), it is advisable to inoculate the culture tubes at the bedside. There was just enough room in this case to carry also a Thoma-Zeiss pipette, a small bottle of Toison's fluid, a couple of slides, and one or two glass pipettes. Messrs. Burroughs & Wellcome have recently made the case of still greater use by adding a drawer at the bottom, and now, with a few minor changes, the case contains practically all that is needed for the collection of clinical pathological material, as well as for several immediate investigations which are of importance in considerations of diagnosis.

In addition to the great convenience of such an arrangement as this, which ensures the juxtaposition of the various pieces of apparatus so that no delay is caused in collecting them when they are required, there is the additional advantage, by no means a minor one, that it enables the worker to use the same apparatus again and again. Not a little of any success which he achieves is due to the facility which comes from close familiarity with his tools. The case, which is of leather, and stoutly made, measures $15 \times 12 \times 9$ inches. The accompanying illustrations show the general arrangement of its contents. Standing vertically in a rack at the back of the case are six culture-tubes (broth, agar, &c.) and two empty sterile tubes plugged with cotton-wool. Below these on the left are two metal spirit-lamps, with screw tops, and on the right are packages of compressed absorbent wool and bandage. On the inner side of the front

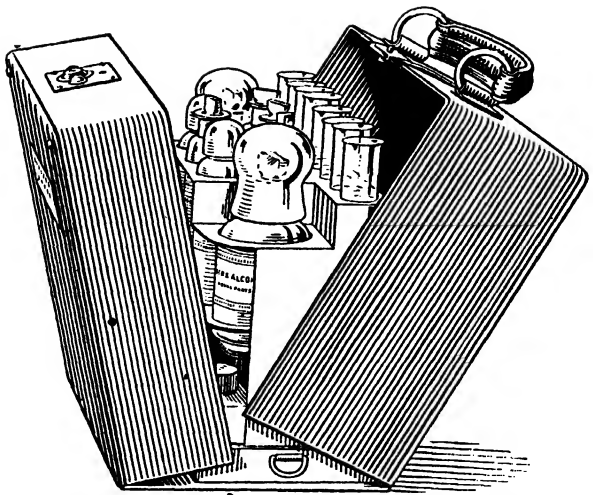


FIG. 1. Hand-case for collection of pathological fluids, cultures, &c.

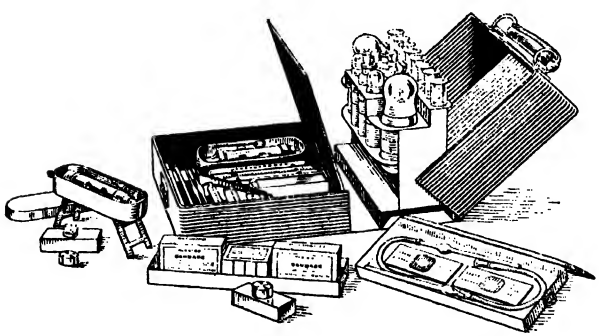


FIG. 2. Pathological hand-case opened to show contents.

of the case, which lets down, there is an all-glass 5 c.c. syringe and a 10 c.c. glass and metal syringe, in metal sterilizers. The smaller sterilizer also contains a small needle for puncturing a vein in performing blood-cultures, and the larger sterilizer contains a longer, stouter needle for lumbar, pleural, lung, or joint puncture. The sterilizers are provided with folding legs so that they can be used for boiling the syringes, &c. A pair of forceps is also provided on the front of the case. The two large stoppered bottles contain respectively, methylated spirit for the lamps and alcohol or acetone for preparing the skin before puncturing it. The five small bottles contain respectively, Toison's fluid for use in blood-counts, Leishman's fluid and distilled water for staining blood or pus films, carbol-fuchsin and sulphuric acid for staining tubercle bacilli in sputum. The drawer at the foot of the case is fitted with grooves for a couple of Thoma-Zeiss pipettes, glass pipettes for collecting blood for Widal's and Wassermann's tests, needles for pricking the skin, microscope slides, cover-slips, and a Thoma-Zeiss counting slide. This drawer is placed horizontally, so that there may be no risk of the Thoma-Zeiss pipette losing any of its contents when filled. To further ensure this, and to avoid evaporation, it is well to stretch a broad rubber band lengthwise round the pipette if the count cannot be at once made.

The case is purposely kept of such a height that if needs be it can be placed vertically in a small travelling bag. The writer is accustomed to carry in a partition of the bag two other useful articles, a ten-ounce stoppered bottle for urine, and a small bottle with a wide neck and a screw top for fæces. Both of these can be sterilized after use. A collapsible microscope, with low and high objective, may be added. The bag will, of course, also contain the few articles in

constant use in purely clinical examinations: stethoscope, ophthalmoscope, laryngoscope, sphygmometer, tape measure, and æsthesiometer.

Armed with this, or with some similar equipment, the clinician is ready for almost any emergency. He is able to collect his materials at the time he sees his patient and to collect them under the best conditions. He is independent of his surroundings, which may fail to provide him with the very things he most requires. Any investigation which is suggested as the result of the examination of the patient, or of a consultation, even though the desirability of such an investigation was not apparent when setting out for his visit, can be provided for forthwith. Not only so, but the apparatus above described permits of not a few very important observations appertaining to clinical pathology being executed at the time of the visit, such as a blood-count, sputum or pus examination, &c., &c. A specimen of any inflammatory exudate may be brought away entire, in addition to the cultures that are made, in the empty sterile test-tubes, and chemical or other investigations can be made later in the laboratory.

During the return journey from seeing the patient it is advisable, if cultures have been made, and the season be cold, to take some means of keeping the tubes warm. This can best be accomplished by placing a bottle of hot water in the bag. Or if the case alone be carried, some warm cotton-wool may be packed against the tubes before the case is closed.

Practical points connected with the actual technique to be observed in collecting the various materials are discussed in the chapters dealing with them. These points need not therefore be referred to here.

# CHAPTER III

## BLOOD-CULTURE

### I. GENERAL

THE examination of the blood by cultivation, for the purpose of discovering the presence of micro-organisms, has become a matter of primary importance in the diagnosis and treatment of septicæmia. Recent researches in connexion with the problems of immunity, and a careful study of the therapeutic effects of sera and vaccines, give considerable promise that at last a door has been opened which may lead to a system of specific treatment in cases of blood infection. It is still necessary, however, to emphasize the need of more frequent investigations of the kind about to be described. These investigations have been too often omitted altogether, or, what is equally to be deplored, have been carried out too late. The reasons for such omission or delay are three. The most general reason has been the failure to recognize how essentially different may really be those cases which are loosely grouped together under the term 'septic'. Another reason has been the great frequency of negative results from the examination, even in undoubted cases of septicæmia. The third reason is the fallacy that the technique of the examination is distressing to the patient.

It is not difficult to combat these objections to the employment of a means of accurate diagnosis. The failure to realize the fact that to label a patient 'septic' goes but a very little way towards establishing a diagnosis is much

to be regretted. For without an accurate diagnosis, and without an early one, the patient's chances of recovery are minimized by denying him the benefit of proper treatment. If the disease be amenable to surgery, it is well that this fact should be ascertained as quickly as possible. If the disease be a true septicæmia the patient should be given, again as quickly as possible, whatever help specific treatment may offer. This help may not, as yet, be very great. It is quite certain, however, that the help cannot but be less if the diagnosis is delayed, and that it is reduced to a minimum if the remedy chosen has no proved relationship to the causal microbe of the disease.

Serum-therapy, hitherto very disappointing when applied to cases of septicæmia, seems to be giving place to vaccination by killed cultures of the micro-organism causing the disease. Perhaps the pendulum has swung too quickly and too far in this matter. Be this as it may, the fact remains that *the treatment of septicæmia, whether by bactericidal serum or by specific inoculation, or by a combination of both of these, must depend for its success upon the isolation from the patient's blood of the micro-organism present, and at as early a stage of the disease as possible.*

There are at present many facts which suggest that a careful study of the clinical and bacteriological aspects of cases of septicæmia is much needed to supplement the knowledge gained by laboratory work in connexion with immunity. Such a study should take note, as its central point of observation, of the bacterial content of the blood from time to time.

## II. INDICATIONS

There is but one indication for blood-culture: the question as to whether or not micro-organisms exist in the blood-stream. Without such an investigation neither the

existence of a septicæmia, nor its nature if present, can be determined.

(i) *The existence of septicæmia.* On clinical grounds alone the diagnosis of septicæmia is impossible.

(*a*) In some cases the disturbance of the functions of the body is so slight that the existence of a general blood infection is not suspected. Yet in these patients a blood-culture may reveal the fact that micro-organisms, even in very considerable numbers, are present in the circulation. In cases of chronic valvular disease this state of things is not at all uncommon. Patients may suffer from infective endocarditis without enough deterioration in their general health to take them to their doctors for advice for a long time. Some dyspnœa of unusual severity, loss of flesh, an anginal attack, joint pains which are thought to be a recurrence of the rheumatism of years ago, an intercurrent illness which is quite unconnected with the old heart mischief —either of these, or some other thing, may bring the patients under close observation, and the presence of fever which does not yield to treatment leads to a suspicion (or should do so) of the real nature of their illness. The course of some cases of infective endocarditis is very prolonged, even up to two or three years. During much of this time the patients may be treated for the less important element of the disease, the valvular defect, while the more fatal element, the infective one, goes unrecognized. The presence of fever in any case of valvular disease is always to be regarded with seriousness, and, if no quite obvious cause of the pyrexia be discovered, a blood-culture should at once be undertaken.

(*b*) In other cases the general disturbance is very considerable, suggesting the presence of septicæmia; whereas, in reality, the patient is suffering from a local infection with an intense degree of toxic absorption. This difficulty

in the diagnosis of local and general infection is an every-day problem in the sphere of obstetrics. The problem is also not uncommon after surgical operations, when performed under difficult conditions and for the treatment of pyogenic infections of various parts of the body. In either of these instances the problem is of fundamental importance in prognosis and treatment.

(ii) *The nature of a septicæmia.* Septicæmia is a disease in which micro-organisms exist in the blood and multiply there. We now know that micro-organisms exist in the blood in several diseases which we are not wont to designate septicæmia. Thus typhoid bacilli are present in the blood during the first week of enteric fever; and pneumococci can often be demonstrated in the blood of pneumonic patients throughout the whole course of the illness. No doubt the prognosis in both of these diseases is influenced by the number of micro-organisms found at any particular time. And the isolation of the specific microbe is in itself a valuable aid to diagnosis (*vide infra*). But it is still convenient to restrict the term 'septicæmia' to the above definition. If this be done the great majority of cases are found to be due to one or other of the common pyogenetic micro-organisms, and run no definite course. The causal microbe can only be determined by means of blood-culture. Some bacteria cause septicæmia very often, such as the streptococcus group. Others cause septicæmia fairly often, such as the pneumococcus and staphylococcus pyogenes aureus. Bacteria of a third group transgress the barrier of the tissues in which they have their usual nidus much less often, and appear in considerable numbers in the blood-stream; such are the gonococcus and the influenza bacillus.

To act as if the causal micro-organism in any particular case of septicæmia is a streptococcus is to substitute a

treacherous assumption for a possible proof or disproof. Pending the proper investigation, it is quite a rational procedure to accept the bias of probabilities and treat the patient for streptococcus septicæmia. But such preliminary treatment should never be considered to replace the necessity for blood-culture. The writer has seen cases both of pneumococcus and of gonococcus septicæmia vigorously treated by antistreptococcus serum for lengthy periods before blood examination revealed the real nature of the infection. Moreover, in order to give antistreptococcus serum a fair trial it is desirable to treat the patient with a serum prepared against a streptococcus having reactions similar to that causing the patient's disease. In order to do this the micro-organism must be isolated and its properties must be investigated. In cases of chronic streptococcus septicæmia it is possible to do even more than this, as the author has elsewhere shown: a serum may be specially prepared by use of the actual micro-organism obtained from the patient.[1] At a time like the present, when much confusion exists as to the proper place of bactericidal sera in the treatment of septicæmia, reported cases of cures effected by these agents should be rigidly excluded from medical literature in the absence of bacteriological evidence of the nature of the causal microbe. Such exclusion entails a little forbearance on the part of the physician who has treated the patient, or a little firmness on the part of the editor who receives the account. If such virtues are not exercised, however, no advance in knowledge can possibly be expected in this direction. The disrepute into which serum-therapy has not unreasonably fallen in the eyes of many medical men is largely due to the reports of the cure of septicæmia in cases in which no evidence of such a condition is forthcoming.

If the argument is sound in the case of serum-therapy

[1] *Lancet*, July 16, 1904, p. 143.

it is equally so in the case of vaccine-therapy. No real advance can be made until blood-culture becomes a recognized routine procedure in all cases of suspected septicæmia.

There are three available methods of examining the blood for micro-organisms.

1. *Blood films* may be made directly and stained by some suitable dye, as carbol-fuchsin, Leishman's or Romanowski's stain. This method demands that for its discovery the micro-organism shall be present in very considerable numbers. It does not enable the micro-organism, if present, to be cultivated. Owing to these two disadvantages the method is not of great value. But as it is so simple and can easily be combined with a differential leucocyte count, it should not be omitted. It is, of course, the only method available when the micro-organism is one which defies attempts at cultivation outside the body, or reproduction of the disease by animal inoculation. Such microbes are the parasites of malaria and sleeping sickness, in the diagnosis of which diseases the study of blood films has proved of such great importance.

2. The second method is that of *animal inoculation*. The patient is bled and some suitable animal is inoculated with the blood. This is obviously not a convenient method, but it may be reserved for special cases.

3. The third method is that of *blood-culture*. Various nutrient media are inoculated with the patient's blood, this being obtained with the strictest aseptic precautions so as to avoid contaminating microbes. This is the method which is by far the most useful.

### III. TECHNIQUE

1. *General.* Formerly the blood was obtained for culture by pricking the ear or the finger. There are two objections to this method: the amount of blood which can be rapidly

obtained is limited, and the risks of contamination of the blood by micro-organisms from the patient's skin, or from the air, are considerable. Both of these objections are almost entirely overcome by taking the blood from a vein in the arm by puncturing this with a sterilized hollow needle, the skin also being sterilized as far as possible. As only a minute area of skin is dealt with in the actual puncture, the risk of cultivating micro-organisms lying on the skin is very small; and as the blood does not come into contact with the air contaminations from that source do not occur at all. The puncture is fraught with very little discomfort to the patient. The writer has performed the operation in quite young children without evoking tears, a fairly severe test.

2. *Preparation of the patient.* In obtaining the blood that arm is chosen in which the largest and most prominent veins are seen beneath the skin of the ante-cubital fossa. The patient lies on his back, near to the edge of the bed, and on the same side of the bed as that of the arm chosen. A good light is essential. The skin is thoroughly cleansed with soap and water, is then rubbed with gauze or cotton-wool soaked in ether or alcohol or acetone, and is temporarily covered with another piece of gauze or lint containing the same solution. Elaborate efforts at complete sterilization of the skin by chemicals are quite unnecessary. Experience shows that they give no better results than the above simple method. Moreover, they are irksome, and suggest to the patient that preparations are being made for some form of major surgery, a suggestion to be avoided. It is well to explain to the patient why it is necessary to use preparations at all.

The arm is now allowed to hang out of the bed and a clean handkerchief is tied round it well above the elbow, so as to cause the veins to stand out prominently. In plethoric

## Plate I

Illustrating technique of Blood Culture.

persons and in most men the bandage is not required. But many of the patients on whom the investigation is made are both anæmic and wasted; these preliminary efforts at rendering a vein full and visible are then well worth attention, as thereby disappointment is often avoided when the puncture is made. In some cases a vein may be distinctly felt when it cannot be clearly seen; the puncture is just as likely to be successful in these circumstances as when the contrary is the case. When the puncture is made the arm is held fully extended, and at right angles to the patient's body.

3. *The preparation of the syringe and needle.* Into the water in which a 5 c.c. glass syringe and needle are boiling a small tabloid of sodium citrate is put, so as to make a solution which contains about 0·5 per cent of the salt. Needle and syringe are now fitted together, and about ·5 c.c. of the boiled citrate solution is taken up into the syringe. This prevents rapid clotting of the blood, and allows of its being squirted into the culture tubes. The syringe is allowed to cool somewhat.

4. *The puncture.* The operator sits facing the patient if the right arm be chosen, but sits with his back to the patient if the left arm be chosen. This position enables the operator to use his right hand for the puncture, and to direct the needle away from the patient's body in either case. The gauze is now removed from the arm and a little alcohol or ether is poured over the skin. The puncture is now made as the solution is evaporating. Care is exercised lest the syringe at any time incline with the needle upwards, as then the piston, which fits the barrel very accurately in the case of the all-glass syringe, may slide a short distance out of the barrel; air is then admitted and possible contaminations also; moreover, the full amount of blood cannot be obtained. The skin is pierced and the direction of the needle is then made parallel with the surface of the skin, so as to avoid

puncturing the posterior as well as the anterior wall of the vein. It is generally advisable to support the vein by the thumb and finger of the left hand as the puncture is being made. The sign of a successful puncture is a flow of blood into the syringe without the employment of suction. When this occurs the piston may be gently removed before the incoming blood until the syringe is full; but a well-fitting glass piston will often be pushed to the top of the barrel by the pressure of the stream of blood unaided by the operator. In any case, suction is useless. Either the needle is in the vein or it is not. If it is the blood will at least flow into the neck of the syringe; if it is not no good can come from using suction. On the other hand, suction may draw air through the junction between needle and syringe (never too free from this possibility), or it may draw a piece of tissue into the needle and block it. If no blood flows the most probable accident is that the posterior wall of the vein is punctured as well as the anterior, this having resulted from neglect to keep the needle almost parallel with the arm, and therefore with the vein. (If the bandage is too near the elbow, or if the patient's sleeve is not turned up sufficiently far, the syringe may not be brought to the right degree of obliquity. To prevent this the arm should if possible be entirely removed from the sleeve.) The right thing now to do is to withdraw the needle a very little; this often leads to an immediate flow of blood. Should it not do so the conclusion is that the needle is not in the vein at all. It is therefore removed still further, but kept just beneath the skin, and a second attempt is made to puncture the vein. If the result is unsatisfactory the needle is completely removed, replaced in the boiled citrate solution, its patency verified—it may be blocked by a bit of tissue—and the whole procedure begun afresh, choosing a different vein.

The syringe being full the needle is promptly removed and the operator's left index finger is pressed against the puncture, and kept there whilst the arm is raised and the bandage is removed. If this be done the skin puncture never bleeds, and needs no dressing. Occasionally a small subcutaneous hæmatoma results if there has been an initial unsuccessful puncture. In this case a firm bandage is applied for a few hours and the arm is kept in a raised position.

5. *Inoculation of the culture media.* The method to be employed depends upon whether the culture tubes can be incubated forthwith, or must be sent through the post prior to incubation.

A. The tubes can be incubated forthwith. The blood is quickly transferred to a series of broth tubes which are in readiness close by. Other media are rarely, if ever, necessary when dealing with the micro-organisms of septicæmia. Some authorities hold that a special medium containing lactic acid is indicated if it be desired to isolate the causal micrococcus of rheumatic fever. The writer has not, however, himself succeeded in isolating from the blood by means of this medium any micro-organism which did not also grow in ordinary broth. Indeed, the writer has never cultivated any microbe from the blood on special media which did not grow equally well, or better, in ordinary broth. This is important, because it sometimes happens that broth is the only culture medium available ; when this is so, no fear need be entertained that a negative result from a blood-culture is due to lack of special or of solid media. The micro-organisms found in the blood are, after all, either capable of vigorous growth in ordinary media or are hæmophilous, in which case the resulting blood-broth medium is excellent for their cultivation.

The writer is in the habit of using half a dozen 10 c.c. broth tubes for each blood-culture, making graduated and known dilutions of the blood in this series by adding a tenth of a c.c. to the first broth tube, a fifth to the second, a half to the third, and so on. The first tube therefore contains blood in the proportion of 1 to 100 of broth. The objects in view are (i) to dilute any antibodies which may be present and which may otherwise prevent growth of the micro-organism, and yet (ii) to have a good bulk of blood in one or two of the tubes, so that if the micro-organisms are very scanty they may still stand a chance of being cultivated. It must be confessed that this method of graduating the dilution of the blood has not hitherto proved to be of much practical value. In the great majority of blood-cultures, growth has taken place equally well in all the tubes, or has not occurred in any. This has been so even in typhoid fever, in which disease it has frequently been said that to obtain growth it is necessary to dilute the blood very freely. In most cases of true septicæmia, and certainly in cases of ulcerative endocarditis, the blood appears to have little or no bactericidal power in regard to the micro-organism causing the disease.

Immediately after inoculation the tubes are rolled vigorously between the hands and are then placed vertically in the warm incubator (37·5° C.), where they are allowed to remain absolutely undisturbed. In a few hours the blood is found to have clotted in all but the very dilute tubes, and the pigment to have sunk to the bottom, leaving a translucent jelly-like clot suspended in the broth. In this clot colonies of any micro-organism present usually develop as isolated whitish masses, easily distinguished and counted. (*Plate* II.)

In a number of cases of blood-culture the writer has incubated one set of the tubes under anaërobic conditions and the other set under aërobic conditions, but has not

# Plate II

Illustrating results of Blood Culture. Two broth tubes showing the development of colonies of *B. influenzæ* in the clot suspended in the broth. The first tube shows a few colonies only in 1 c.c. of blood; the second shows a large number of colonies in the same quantity of blood.

*To face p.* 24.]

hitherto obtained growth anaërobically in any case where it did not occur aërobically.

If a full laboratory equipment is at hand it is better, for quantitative purposes, to mix the blood with melted agar, and to pour plates of the blood-agar thus produced. In this way the separate colonies are more easily counted. But the writer has on several occasions failed to obtain growth on plates where it occurred in broth. For this reason, for the reason that sterile Petrie dishes are not always available, and for the reason that in the present stage of our knowledge proof of the existence of septicæmia is of more importance than an estimate of the number of bacteria present in the blood, the writer considers the simple method of culture in broth tubes to be the more valuable.

The various steps in performing blood-culture have purposely been described in detail. On paper the process seems a lengthy one. In actual practice, however, it occupies less than half an hour, including the preparation of the patient and the inoculation of the tubes.

B. The tubes must be sent through the post. In this case gelatin tubes are used instead of broth tubes. The gelatin is melted by placing the tubes in water at a temperature of 30° C. The blood is then well mixed with the medium in the manner described under A, and the tubes are allowed to cool down to the temperature of the room. When the gelatin has solidified, the tubes are posted to the pathologist. This method cannot be adopted in very warm weather unless the tubes are packed in ice or in a Thermos flask.

6. *Examination of the culture tubes.* This is a matter of bacteriological technique, and therefore does not come within the scope of this book. It may, however, be well to remind the bacteriologist that the object of the blood-culture is to give every possible facility for any micro-

organism that may be present to reveal itself by growth. A few practical points in this connexion may not be amiss. (*a*) If there is no apparent growth in twenty-four hours, either to the naked eye or by use of a hand lens, it is a good thing to roll one or two of the tubes again, thus diluting the blood, which has sunk to the bottom of the tube, a second time; a minute colony that may have formed in the bottom of the tube is thus allowed to inoculate the supernatant parts of the medium. (*b*) The tubes must be re-examined at intervals up to three or even four days: growth is sometimes delayed as long as this. (*c*) The tubes must never be set aside as sterile without examination of a little of the sediment under the microscope. (*d*) Care must be taken that the temperature of the incubator is well up to 37·5° C.

### IV. INTERPRETATION OF RESULTS

If the method of blood-culture described above be adopted contaminations will be found to occur very rarely. If they do occur, their elimination is easy. The commonest contaminations found in blood-culture work are *staphylococcus epidermidis albus* from the skin and various *sarcinæ* from the air. Less common than these are diphtheroids (xerosis, &c.), probably also from the skin. The bacteriologist will suspect a staphylococcus to be a contamination if it occur in one or two only of the tubes, and if it exists chiefly as diplococci in the broth. He will prove it to be *S. epidermidis* by the absence of acid formation in mannite, by the slow liquefaction of gelatin and by the absence of pathogenicity for mice.

Unless the same micro-organism can be demonstrated in each of the tubes, considerable distrust must be entertained

that it has come from the blood, unless its characters make this conclusion practically certain.

With due regard to the question of contaminations, the pathologist will report the presence or absence of micro-organisms in the cultures, and if present he will state their character and give some idea of their numbers. This report must be taken in conjunction with the clinical features of the case, and with any blood-tests which may have been undertaken. Valuable diagnostic knowledge though it is, the mere demonstration of micro-organisms in the blood, apart from other facts connected with the case, gives little information in regard to prognosis or treatment. As already mentioned, it is known to-day that micro-organisms exist in the blood in the course of more disease processes than was formerly thought to be the case. The almost hopeless prognosis to which their discovery once led the physician no longer holds good. The associated condition is of fundamental importance in any conclusion with regard to prognosis. It must be remembered that the typhoid bacillus can be demonstrated in the blood during the first week of a large number of even mild cases of enteric fever; also that the pneumococcus can similarly be demonstrated in the blood in many cases of pneumonia. In both these cases, however, the number of micro-organisms is usually quite small. It may be confidently said that the prognosis is bad in proportion to the number of micro-organisms present. If, for example, there be evidence of ulcerating endocarditis in pneumonia, the number of pneumococci in the blood is generally great, and the prognosis is as grave as it can be. In typhoid fever, the later in the course of the disease that bacilli are found in the systemic blood-stream, the worse the prognosis. The writer is of opinion that the isolation of the bacillus from the blood after the tenth day constitutes a very bad prognosis.

# CHAPTER IV

## THE HISTOLOGICAL EXAMINATION OF THE BLOOD

### I. GENERAL

THE histological examination of the blood must nowadays be accorded a very important place in the diagnosis of disease. Instruments capable of a fair degree of precision have been introduced for the purpose, and it is easy to attain such facility in the use of them that a set of observations may quickly be made, and the results obtained by two different observers in the same case should vary by no appreciable amount. A sufficiently accurate leucocyte count, which is perhaps the most generally useful of all the observations made upon the blood in differential diagnosis, can be carried out in about twenty minutes; a full count of red and white cells can be made in half an hour; and a complete histological blood examination can often be accomplished within an hour. This chapter will be devoted to a consideration of those methods of examination, other than bacteriological, which have been proved to be of service in the diagnosis and prognosis of disease. The rule already observed, of omitting all details connected with laboratory methods, will still be followed. It may be taken for granted, however, that the estimation of hæmoglobin and red cells, and especially the leucocyte count, have now become matters of bedside examination; these will therefore be dealt with both as regards methods and results.

## II. THE AVAILABLE DATA

The following are the chief facts which may be elicited by a clinical blood examination :

(i) *Hæmoglobin* : the relative amount present.

(ii) *Red cells* : the absolute number present in a given volume of blood ; the shape and size of the cells ; the staining properties of the cells ; the presence or absence of nucleated cells.

(iii) *White cells* : the absolute number present in a given volume of blood ; the characters of the cells and the number of each kind (differential count).

(iv) *The Colour Index*, i. e. the relation between the amount of hæmoglobin and the number of red cells.

Some other data are available, such as the number of blood platelets, the coagulation time, the viscosity, and the presence of abnormal chemical constituents. These data are of far less importance in practice than the above.

## III. METHOD OF OBTAINING THE BLOOD

This is extremely simple. The lobe of the ear, or the end of the finger, is well rubbed with cotton wool soaked in ether or spirit, or is merely washed with soap and water, and is then rubbed dry. This process serves both to cleanse the skin and to cause flushing of the vessels. A bold prick is now made with a sharp bayonet-shaped needle, and the blood which oozes from the puncture is collected as described later. Should blood not ooze freely the ear or finger is squeezed, the pressure being applied *at a distance from the prick* so as to avoid forcing out an undue proportion of serum. The blood thus obtained may be utilized in three ways :— (*a*) It may be examined as a fresh specimen under the microscope. (*b*) It may be spread into films, which are

allowed to dry, and are then stained by Jenner's or Leishmann's solution, or by Ehrlich's tri-acid dye. (*c*) It may be collected into one or more of the special pipettes used for the purpose of certain quantitative estimations to be described later.

## IV. THE MICROSCOPICAL EXAMINATION OF FRESH BLOOD

This method is not of very extended value in practical medicine. It should, however, be used more frequently than it is, especially when other methods are not available. It is of service in *suggesting* other methods of examination. The following are the principal points that can be observed in the investigation of a specimen of fresh blood. (1) The *malaria* parasite may be seen and its development may be watched. (2) The abnormal shapes and sizes of the red cells may be studied in *pernicious anæmia*. (3) The presence of excessive numbers of white cells may suggest the existence of *leukæmia*, or, in marked cases, of *leucocytosis*. (4) Rouleaux formation and fibrin deposit may be seen to be normal or otherwise.

The recent introduction of dark-ground illumination is of great service in the search for the *spirochæte* of syphilis. A wider application of this mode of examination may prove it to be of considerable help in the study of the blood in disease.

## V. THE PREPARATION OF BLOOD FILMS

Blood films should always be prepared whenever a 'blood-count' is undertaken. The films may not be required, or may be found to be normal, but it often happens that they are required to complete the conclusions suggested by the 'count'. The films may be made either on large cover-slips or on slides. In either case the glass must be quite

clean and free from grease. This is secured by boiling the slips or slides in strong nitric acid, rinsing in running water, and keeping under absolute alcohol. If cover-slips are used, a slip is taken in a pair of forceps, allowed to touch the drop of blood at its centre, and is then dropped carefully, face downwards, upon a second slip. The two are separated by a sliding movement as soon as the drop of blood has spread to the edges of the slips. A very thin film of blood is aimed at. If slides are used, the short edge of a slide is allowed to touch the drop of blood at its centre, and is then placed in an inclined position upon a second slide lying horizontally. When the drop of blood has spread along the whole of the edge of the first slide, this is drawn steadily along the horizontal slide, upon which a thin film of blood is thus deposited. Slips and slides are allowed to dry in the air, without the aid of heat.

## VI. THE HÆMOGLOBIN

The colouring matter of the red blood corpuscles is measured as a percentage, the standard (100 per cent) being somewhat arbitrarily chosen to represent the relative amount usually found in healthy adult men. Many forms of apparatus have been devised for the purpose of hæmoglobin estimation. The writer considers that Haldane's modification of Gower's hæmoglobinometer (Fig. 3) best combines accuracy with convenience of working, and he has shown that the personal equation in the use of the instrument is quite small as compared with that introduced by Fleischl.

1. *Estimation of Hæmoglobin.* The liquid in the tube *A* serves as the standard colour. It consists of a 1 per cent solution of blood containing the average percentage of hæmoglobin found in healthy adult men. The solution is

saturated with carbon monoxide and hermetically sealed. This renders the colour permanent. The tube *B* has the same internal diameter as *A* and is graduated in percentages. In using the instrument a little water is first placed in the tube *B*, care being taken to avoid putting as much water as will dilute the blood too much. Water to the 20 per cent mark can almost always be allowed. Blood is now sucked up into the capillary tube *D*, which must be clean and dry, as

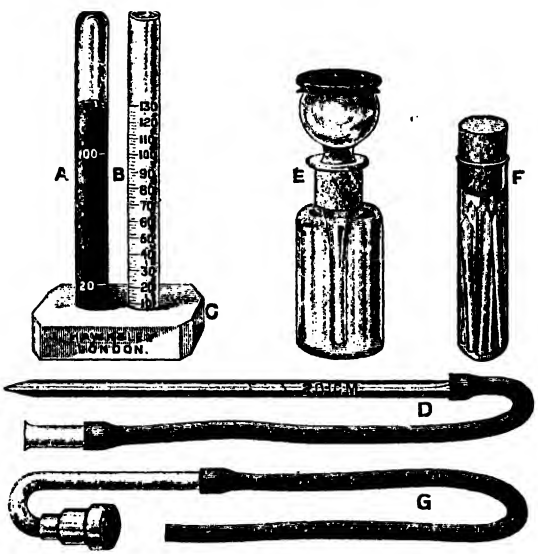



FIG. 3. Haldane's hæmoglobinometer.

far as the mark (=20 c.mm.). The point of the pipette is wiped, and any excess of the column of blood above the mark is removed by dabbing the end of the pipette on a piece of absorbent paper or cloth. The point of the pipette is then inserted just beneath the surface of the water in the tube *B*, and the blood is gently blown out. It sinks to the bottom. The pipette is kept in the same position and is rinsed several times with the water lying above the blood. The tube *B* is now rolled rapidly between the hands to mix

the blood and water, and a stream of coal gas is passed into it for a few seconds by means of the rubber tube and cap *G*, which is made to fit over a gas burner. As the rubber tube is withdrawn, with the gas still passing, the end of *B* is closed with the forefinger, and by repeated inversion the liquid is made to pass up and down the tube several times so as to saturate the hæmoglobin with CO. Water is now added drop by drop from the drop bottle *E*, the tube being inverted after each addition. This procedure is repeated until a point is reached at which the tints of the liquids in the two tubes are equal. It is desirable that as much water as is safely possible should be added in the first instance, so that the subsequent additions may be few; if the manipulations are prolonged the contents of the tube become heated, and spurting then occurs when the finger is released from the top after the process of inversion. In judging of the equality of the tints the tubes should be held against the light from the sky, or, if artificial light be used, against the light from an opal glass shade. The tubes should be repeatedly transposed—right to left and left to right—to avoid error of judgement. Two other points in the technique conduce to accuracy of results: covering the tops of the two tubes by the hand so that it cannot easily be seen which is the standard and which the trial tube, and striking the mean between the first reading at which the two tints seem to be equal, and the reading (obtained by further slight addition of water) at which the tints are obviously unequal.

2. *Increase in hæmoglobin.* This is occasionally found in moderate degree as a physiological condition in both men and women, but especially in the former. It may merely denote 'rude health', such as follows a holiday spent in the open air, or it may carry no special significance at all. The pathological conditions in which relative increase of

hæmoglobin occurs are (i) congenital heart disease and (ii) splenomegalic polycythæmia (' chronic cyanosis with enlarged spleen and polycythæmia '). The writer has found the condition also present in (iii) diabetes insipidus, suggesting that the blood is sometimes inspissated in this disease.

3. *Decrease in hæmoglobin.* A slight decrease in hæmoglobin may be physiological in some town-dwellers who are still in all ordinary respects in good health. As a pathological state it is present in every case of anæmia. Taken in conjunction with the number of red cells the amount of the decrease gives important information as to the type of anæmia that is present. In itself the figure is a measure of the degree of the anæmia, but gives no clue to its type.

## VII. THE NUMBER OF RED CELLS

1. *Enumeration.* This is best done by the use of a Thoma-Zeiss pipette and counting chamber (Fig. 4). A pipette should be chosen which has the 101 mark placed well above the neck of the bulb. The pipette is thoroughly cleaned by drawing through it first a mixture of dilute acetic acid and alcohol and afterwards one of pure ether. It is then held near the fire, when the evaporation of the ether will leave a perfectly dry surface inside the bulb and capillary tube. Proof of the dryness of the interior of the pipette is given by the freedom of the glass bead within the bulb. The blood is sucked up the capillary tube to the mark 1 (=1 c.mm.). The nose of the pipette is quickly wiped on a bit of blotting paper or cloth, so as to clean off any excess of blood. If by chance the mark on the pipette has been exceeded by the column of blood the height of this column must at the same time be reduced by lightly touching the blotting paper once or twice with the point of the pipette held vertically against the paper. Immediately the desired level is obtained, the point of the

pipette is dipped beneath the surface of some appropriate diluting fluid and this is drawn up into the bulb until the level of the mixture reaches the 101 mark. At this point the suction is stopped, the pipette is withdrawn from the fluid and is rapidly rotated for half a minute to ensure thorough mixing of the blood and diluting fluid. The fluid in most general use for diluting the blood is Toison's fluid, which consists of a mixture of water, glycerine, sulphate and chloride of sodium, tinged with methyl violet. A very

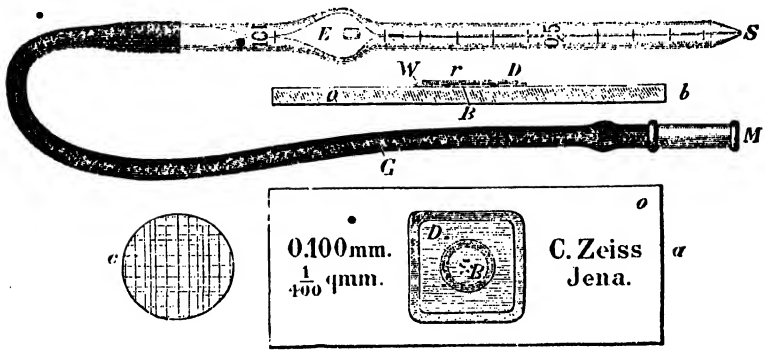



Fig. 4. Thoma-Zeiss pipette and counting chamber.

convenient mode of preparing the fluid is to use the 'soloids of Toison's fluid' supplied by Messrs. Burroughs, Wellcome & Co. This fluid stains the leucocytes a faint violet colour, but leaves the red corpuscles almost unstained. The process of mixing being completed, about one-third of the contents of the bulb are now blown out, and a drop of the remainder is placed upon the centre of the cell on the counting slide. The specially ground cover-slip is put over the drop, which should be of such size as just to fill the cell when the cover-slip is gently pressed down. If the drop is too large, and a portion of it overflows into the small moat round the cell, the slide and slip must be thoroughly cleaned

and a smaller drop of the mixture must be used. The corpuscles are now allowed to settle and they are then counted. Fig. 5 represents the kind of appearance presented by the field of the microscope when one-sixth objective and No. 2 eye-piece are used. The corpuscles lying over the greater portion of the figure have been omitted for the sake of clearness. The arrow indicates the order of the small squares on the slide which it is recommended to

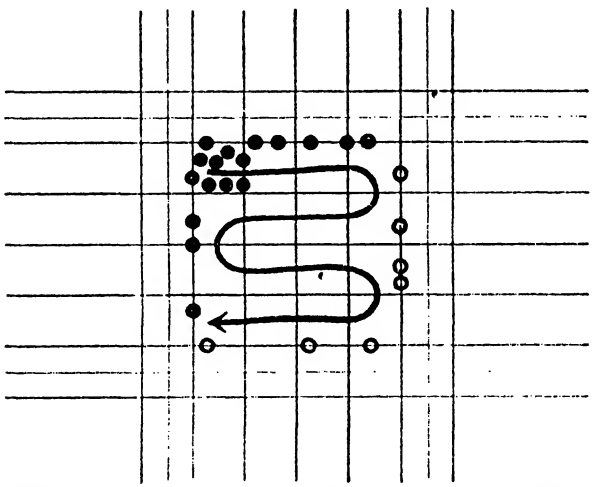


FIG. 5. Showing method of counting cells in large square. Cells marked are counted; cells marked O are not counted.

follow in making the count. With regard to cells lying on the lines, a useful convention is to count the cells lying on the top and left-hand lines, and to omit those lying on the bottom and right-hand lines of the squares. Thus, in the diagram, cells marked in black are counted, those marked in white are not. In this way all the cells will be counted that lie within the large square, and half of those that lie partly within and partly outside it. A large square includes sixteen small squares. The more squares counted the more accurate the result. Experience shows that counting five large squares

(i. e. $16 \times 5 = 80$ small squares) yields a result that is very trustworthy. The calculation is made as follows. The small square is $\frac{1}{20}$ mm. in length and in breadth, and the height of the cell is $\frac{1}{10}$ mm. The cubic contents of each square when covered by the slip are therefore $\frac{1}{20} \times \frac{1}{20} \times \frac{1}{10}$ c.mm. If $x$ be the average number of cells lying on each small square, the number of cells present in 1 c.mm. of diluted blood is therefore $x \times 4000$. The number in 1 c.mm. of blood is therefore $x \times 400{,}000$.

The number of red cells present in the blood of a healthy adult man is about 5,000,000 per cubic millimetre. The figure is usually a little lower than this in healthy women (4,500,000). It is not at all uncommon to find the number somewhat over 5,000,000 in healthy young men. If there is no other unusual feature about a blood examination, any figure lying between 4,500,000 and 5,500,000 may be taken as being within the range of health.

2. *Increase in the number of red cells* (erythrocytosis; polycythæmia). This is found in the same conditions mentioned as causing increase in hæmoglobin,—congenital heart disease, chronic cyanosis with splenomegaly, and diabetes insipidus. In *morbus cæruleus* the count of red cells may rise as high as 12,000,000. This erythrocytosis in congenital heart disease serves sometimes as a point of diagnostic significance in a case in which there is doubt whether the valvular defect is congenital or acquired. In splenomegalic polycythæmia, a rare but well-defined condition, the red cells usually vary between 6,000,000 and 10,000,000. In one case under the care of the writer, striking oscillations were noted in the count of red cells, and it was observed that the patient's general condition was much better when the count was high than when it was low. A count of 6,000,000 occurred with dyspnœa, swelling of the ankles, and malaise;

rest, X-ray applications to the spleen, and a course of arsenic were followed by great improvement in general health, together with a rise in the count of red cells to 8,500,000.

3. *Decrease in the number of red cells* (erythropænia, oligocythæmia). A much more common state of things, and one which, in more or less degree, accompanies almost every disease, and constitutes a cardinal feature in all forms of anæmia. The decrease in red cells is not usually very marked in the symptomatic anæmias ; it is a more significant feature in chlorosis ; it attains a degree of great importance in pernicious anæmia, in which condition the numbers may reach a very low level. Counts of less than 500,000 are not very uncommon in the late stages of this last-named disease ; the writer has seen a case in which the number of red cells sank to 292,000.

## VIII. THE COLOUR INDEX

1. The proportion of hæmoglobin to the number of red cells present in a specimen of blood is termed 'the colour index'. The term is better than 'corpuscular richness', which admits of ambiguity. Hæmoglobin is estimated as a percentage ; red cells are counted in absolute numbers ; to obtain the index it is therefore necessary to reduce the number of red cells to a percentage, 5,000,000 being taken as 100 per cent. Thus

$$\text{C. I.} = \frac{\text{per cent of hæmoglobin}}{\text{per cent of red cells}} = \frac{100}{100} = 1 \text{ (in health).}$$

Just as slight variations in the amount of hæmoglobin and in the number of red cells occur in a state of comparative health, so slight changes in the colour index also occur without any other evidence of disease. Indeed it is rare to find a colour index of 1·0 in healthy persons ; it is more often a little less than 1·0, because the hæmoglobin tends so often to be less than 1·0 by most of the instruments used in its estimation.

2. *Increase in the colour index.* This occurs in very few conditions. In order that it shall obtain the reduction in red cells must be proportionately greater than the reduction in hæmoglobin, and this is seldom seen except in *pernicious anæmia*, in which condition it is often a striking feature. It may be as high as 2 or even higher. The colour index is sometimes raised in leukæmia.

3. *Decrease in the colour index.* This is seen in the great majority of cases of secondary (symptomatic) anæmia, as well as in the hæmorrhagic anæmias and in chlorosis. In the last-named condition, in which the reduction in hæmoglobin is the salient feature, a low colour index marks off the condition from pernicious anæmia very definitely.

## IX. TYPES OF ANÆMIA

Having considered the quantitative data connected with the hæmoglobin and with the red cells, it is now possible to refer briefly to the various conditions spoken of generally under the term 'anæmia'. It should be understood that the word 'anæmia' merely connotes these two factors and their relations to each other; the number and kind of leucocytes present do not enter into the question.

There are three main types of anæmia:

1. *Post-hæmorrhagic type* (acute anæmia). Colour Index = 1. That is, a proportionate reduction occurs in hæmoglobin and in red cells. The reduction only remains proportionate, however, for a short time. In a few days after a large hæmorrhage, the red cells are found to have increased out of proportion to the increase of colouring matter; the colour index therefore falls and the type of anæmia approaches (2).

2. *Chlorotic type.* Colour Index $< 1$. There is a proportionately greater reduction in hæmoglobin than in red

cells. This type of anæmia includes chlorosis and all the so-called 'secondary' or symptomatic anæmias.

3. *Pernicious type.* Colour Index 1 or >1. There is great reduction in both hæmoglobin and red cells, but especially in red cells. The actual figures are therefore low, but the colour index remains high. This type of anæmia includes the so-called idiopathic pernicious anæmia, and some cases of secondary (symptomatic) anæmia occurring in malignant disease of the stomach, severe lead-poisoning, anchylostomiasis, and some other parasitic diseases.

## X. QUALITATIVE CHANGES IN RED CELLS

In health the erythrocyte is a non-nucleated biconcave disk measuring, with great constancy, about 7 $\mu$ in diameter. It stains fairly well with acid dyes (oxyphilic). In severe grades of anæmia the following abnormal features may be observed:

1. *Small cells* (microcytes). 2. *Large cells* (macrocytes). No special significance is to be attached to these cells. 3. *Nucleated cells.* These are of two distinct kinds, and it is essential to recognize these two varieties, because they possess a different significance. (*a*) The nucleus of the cell is relatively small in proportion to the protoplasm, and stains deeply with basic dyes; the nucleus may be lobed. This cell is termed *normoblast.* It is seen in the blood soon after a very severe hæmorrhage, is common in the anæmias of childhood, and in marked degrees of anæmia in adults. Its presence is not of bad prognostic import. (*b*) The nucleus of the cell is relatively large in proportion to the protoplasm, and stains feebly with basic dyes. Sometimes there is a narrow zone around the nucleus which scarcely stains at all; and the protoplasm itself often stains badly. This cell is termed *megaloblast.* It is seen only in the most severe

grades of anæmia of the pernicious type, and according to many observers its presence indicates that the case is one of primary pernicious anæmia.

4. *Abnormal shapes* (poikilocytes). Instead of the normal disk a large variety of distorted shapes may be observed in anæmic blood, pear-shaped and battledore-shaped cells, and, in extreme cases, cells with scarcely any contour at all. These marked changes are again associated chiefly with pernicious anæmia.

5. *Abnormal staining.* This may be a uniformly feeble staining reaction, or it may be a variable depth of staining in different cells (polychromatophilia). Abnormal staining properties are common in cells of abnormal size and shape.

## XI. THE NUMBER OF WHITE CELLS

The fact has already been mentioned that anæmia is a condition in which the white cells of the blood are not necessarily affected. In one very important disease of the blood, however—*leukæmia*—the notable feature is a considerable increase in the number of white cells, and there is nearly always an associated anæmia, sometimes of considerable degree. Of much greater importance even than leukæmia, in connexion with the white cells, are the many conditions in which these cells undergo a symptomatic increase or decrease in number, conditions which have their diagnosis much facilitated by an accurate estimation of the number of white cells present. So important, therefore, is this estimation, that the use of the Thoma-Zeiss pipette becomes to-day an essential part of the practitioner's clinical examination in many cases which he investigates.

*Enumeration of white cells.* This is undertaken in the same manner as the enumeration of the red cells (p. 34). If it is thought unnecessary to count the red as well as the white cells, a solution of acetic acid (0·5 per cent) tinged

with methyl green may be used for the diluting fluid instead of Toison's fluid. This solution renders the red blood-cells invisible, but makes the white cells more conspicuous; the latter are therefore more easily counted. One advantage of the acetic acid solution is its permanency; unlike Toison's fluid, which is apt to develop yeast cells, it undergoes no change on being kept.

In performing a count of white cells it is desirable, for purposes of accuracy, to cover as large an area of the ruled slide as possible. Yet it is also desirable to complete the count within a reasonable time. The writer adopts the following convention, having found it, from long experience, to be very accurate and yet speedy. Having filled the counting cell with the diluted blood, the tube of the microscope is adjusted in length so that the field of the $\frac{1}{6}$ or $\frac{1}{7}$ objective just includes the length of a convenient number of small squares in its diameter. The most convenient number of lengths so included is 8. If this arrangement be adopted the size of the field, being $\pi r^2$, is equivalent to $\frac{22}{7} \times 4 \times 4 = 50\frac{2}{7}$ squares. In view of the large number of squares that can be easily counted by this method, the odd $\frac{2}{7}$ square is neglected and the field is taken to include 50 squares. Twenty fields therefore include 1,000 squares, and this is the number which it is advisable to count. It should be noted that the slide may be moved past that part on which the squares are marked: the area of the field will be still the same. The calculation is very simple. The total number of cells counted in the 20 fields, divided by 1,000, gives the average number of cells per square. This, multiplied by 400,000, gives the number of white cells per cubic millimetre of blood. If this method be adopted, and 20 fields are always counted, the total number of cells counted may be multiplied by 400 to give the result.

The number of white cells present in the blood of adults in health varies between 6,000 and 8,000. There is a physiological increase during the process of digestion, and it is customary to say that the number should not be below 6,000 before a meal nor above 8,000 after a meal. The height of the 'digestion leucocytosis' appears to occur about two hours after taking food.

Quantitative changes in the white cells are much more complex than in the case of the red cells, because there are different kinds of white cells in the blood, and the increase or decrease may affect different varieties of cells. A blood-film should always be taken at the same time that the Thoma-Zeiss pipette is filled; it may then be seen, by making a 'differential count' of the white cells, which variety of cell is really increased or decreased in number. In the great majority of cases in which there is a symptomatic increase in the white cells, it is the particular cell called by hæmatologists the 'polymorphonuclear' cell, or, for short, the 'polymorphous' cell, which contributes the increase. So, also, it is usually this cell which is concerned when the total number of white cells in the blood is decreased. The polymorphous cell is the cell present in greatest numbers in healthy blood. For this reason it is spoken of simply as the 'leucocyte', in contradistinction to the 'lymphocyte' and the 'eosinophil' cell, which are present, at least in adults, in fewer numbers.

The differential white cell count in healthy adult blood is as follows:—

| | percentage | number per c.mm. |
|---|---|---|
| Polymorphonuclear cell (the leucocyte) | 65–75 | 5000 |
| Small lymphocyte | 20–25 | 1500 |
| Large lymphocyte | 3–5 | 300 |
| Eosinophil | 2–4 | 150 |
| Basophil | 0·5 | 50 |

## XII. LEUCOCYTOSIS

An increase in the number of white cells, when this increase affects the polymorphous cell only, is termed a *leucocytosis*. A leucocytosis is always symptomatic of some other disease process. As already stated, the presence of this condition is usually decided merely upon a count of the total cells, without a differential count; but this mode of procedure involves a possible fallacy, because it cannot be said with certainty, in counting the white cells by the Thoma-Zeiss method, which are leucocytes and which are lymphocytes, &c.

A leucocytosis is an important clinical fact, and its demonstration frequently assists greatly in questions of diagnosis and prognosis. Instances of leucocytosis may be divided into two classes:

1. *Physiological leucocytosis.* This is seen in new-born infants, during pregnancy and after parturition, during digestion, and after cold bathing and exercise.

2. *Pathological leucocytosis.* A large number of morbid states lead to an increase in the leucocytes of the circulating blood. These states may be grouped as follows:

(i) *Acute general infections.* Probably the only known exceptions are typhoid fever, Malta fever, influenza, malaria, measles, and general tuberculosis. In all other specific fevers a rise in the number of leucocytes takes place. The rise is very marked in pneumonia ('lobar' and 'lobular') and in pneumococcus infections of all kinds. It is usually well marked in rheumatic fever, scarlet fever, and diphtheria. All forms of septicæmia show a leucocytosis.

(ii) *Acute local infections.* So-called 'septic' conditions are all of them accompanied by a leucocytosis. Thus, in erysipelas, cellulitis, acute abscess, tonsillitis, otitis media, appendicitis, pyelitis, and a large number of other acute

infections, a leucocytosis is almost invariable. Moreover, when local inflammatory conditions complicate the specific fevers mentioned under (i), which are otherwise unaccompanied by leucocytosis, there is a rise in the number of white cells: peritonitis in typhoid fever, broncho-pneumonia in measles, cholecystitis in influenza, or meningitis in tuberculosis, are all productive of leucocytosis. The diagnostic value of this fact is obvious.

The intensity of the leucocytosis varies directly with the tendency to pus formation at the seat of the local inflammation. Thus, a count of 20,000 or over in a case of appendicitis is highly suggestive of abscess formation. If the leucocytosis is seen to rise day by day it may still more confidently be surmised that pus is forming.

(iii) *Chronic infective conditions* are associated with a leucocytosis, but this is usually less in degree than is seen in acute infective processes.

(iv) *Malignant disease.* Leucocytosis occurs in practically all cases of malignant disease, but is specially marked in those cases in which the growth is increasing rapidly. If ulceration is present this element tends to produce a still higher leucocyte count.

(v) *Hæmorrhage.* The initial decrease in leucocytes occurring immediately after a hæmorrhage is followed by an increase during the stage of 'reaction'.

(vi) *A terminal leucocytosis* may almost be said to be a constant antecedent of death, even when a leucopœnia was for some reason a part of the patient's disease, as in pernicious anæmia.

*Prognostic value of leucocytosis.* The presence of leucocytosis is not only of service in assisting diagnosis, it also serves as a valuable factor in estimating prognosis. Generally it may be said that if a cause of leucocytosis be

present the higher the count of white cells the better the outlook for the patient. If, however, the infection is a mild one, and the general condition of the patient is good, a slight leucocytosis is not an unfavourable sign. One of two conditions may be surmised if the leucocytosis is only trivial in a case in which a cause of leucocytosis is known to be present and the infection is marked: either the resistance of the patient is low, or the degree of poisoning is very severe. Both conditions may concur in the same case. This is an important point in judging the prognosis in a case of pneumonia. In a patient in whom the disease is taking a favourable course the leucocyte count rises steadily until the day of the crisis, at which time it becomes very high (20,000–40,000). If, however, the patient is debilitated, or is an alcoholic subject, or if the degree of infection is very severe, this critical leucocytosis is apt to be absent. The same remark applies to cases of broncho-pneumonia in children, in which disease, when the course is favourable, an enormous leucocytosis may be observed. Dr. Salmon, one of the writer's former house-physicians, recorded a leucocyte count of 136,000 in such a case. A film of this child's blood showed a condition at first sight resembling leukæmia; but the differential count proved the condition to be a symptomatic leucocytosis.

It has already been pointed out that a lower count of white cells is usually seen in generalized than in local pyogenic injections. Thus, in septicæmia, from whatever cause, the leucocytosis seldom exceeds 15,000; whereas in local infections proceeding to suppuration it is quite common to find a count of 30,000–50,000, even in adults. Again, a difference is seen in different types of septicæmia; thus it is unusual to find counts above 15,000 in chronic cases which are slowly losing ground, such as cases of chronic

malignant endocarditis; whereas in acute cases, with evidence of good reaction on the part of the patient, the count is often a good deal higher.

### XIII. LEUCOPŒNIA

A decrease in the number of white cells is a condition termed *leucopœnia*. The term is properly confined to a decrease in the polymorphonuclear cell—a point that can only be accurately determined by a differential count of white cells. Such a differential count, in a case of leucopœnia, yields what is sometimes spoken of as a 'relative lymphocytosis', because the percentage of lymphocytes is raised. But a statement of the numbers of the different white cells will always be made by the pathologist in absolute figures, for it is these alone that are of definite value. Leucopœnia occurs in the following conditions:

(i) *Acute hæmorrhage.* Here the reduction in white cells is concerned with all varieties; it is not, therefore, strictly speaking, a true leucopœnia. The reduction is only found for a short time—a matter of hours—being soon replaced by a leucocytosis *vide supra*).

(ii) *Pernicious anœmia.* An important cause of leucopœnia. In a typical case the total count of white cells is reduced to 2,000–3,000.

(iii) *Splenic anœmia.* A similar state of things obtains.

(iv) *Acute specific infections.* So far as our present knowledge goes the following is a complete list of the infective processes in which the leucocytes in the circulating blood are reduced in number: *malaria, Malta fever, typhoid* and *paratyphoid fever, measles, influenza,* and *general tuberculosis.* In some acute infections by *B. coli*, such as cholecystitis, the author has shown that a leucopœnia also occurs. It will be readily seen that the diagnostic value of a leucopœnia in

an acute febrile illness is very great. In a febrile patient who has not lived out of England, and in whom, therefore, malaria and Malta fever can be excluded, a leucopœnia is strongly suggestive of either typhoid fever or influenza. If the pyrexia has lasted for longer than five days the probability of typhoid fever is great. The association of leucopœnia with a partial Widal reaction must be accorded great weight in the diagnosis of typhoid fever. If there is no positive Widal reaction, the discovery of a leucopœnia should lead to a blood-culture being undertaken, for in these circumstances the typhoid bacillus may often be isolated from the circulating blood.

## XIV. LYMPHOCYTOSIS

This term is applied to a symptomatic increase in the lymphocytes of the blood. In *children*, even in health, the lymphocytes exist in larger numbers than in adults, and they are absolutely increased in most conditions which lead to leucocytosis at this stage of life. In addition a marked lymphocytosis is usually seen in *pertussis* (up to 20,000–40,000), in *active rickets* and in some forms of *tuberculosis*. In both children and adults there may be a lymphocytosis in *Hodgkins' disease*, though this is by no means invariable.

## XV. EOSINOPHILIA

The number of coarsely granular oxyphil cells present in healthy blood varies considerably, but rarely exceeds two per cent. (± 120 per c.mm.). An increase in eosinophil cells occurs in the following conditions :

(i) *Parasitic diseases.* The presence of any parasite, whether in the intestine or elsewhere, may be associated with eosinophilia. Thus, *tœnia mediocanellata*, *oxyuris*

*vermicularis* and *ascaris lumbricoides* are common causes of this blood change. The presence of one or other of these worms may sometimes be suspected by finding an increase in the eosinophil cells whilst undertaking a blood-count. In this way the cause of an obscure illness is not seldom brought to light. In *hydatid disease* of the liver eosinophilia is frequently present: the nature of a tumour in this organ may therefore be suggested by a blood examination.

(ii) *Skin diseases.* In *pemphigus*, when not due to a local infection, eosinophilia is common; it has also been described in *psoriasis*, *urticaria*, and other skin affections.

(iii) *Asthma.* During the paroxysms, and for a short time afterwards, there is often a considerable increase in the eosinophil cells of the blood. This may serve as a distinction between true asthma and certain other forms of dyspnœa (as in uræmia). Reference has been made in chapter v to the presence of large numbers of eosinophil cells in asthmatic sputum.

## XVI. LEUKÆMIA

Two main types of leukæmia are recognized, according as the principal white cell present in the blood is the myelocyte (*myelocythœmia*) or the lymphocyte (*lymphocythœmia*). Just as there is a symptomatic lymphocytosis which is not lymphatic leukæmia, so there is a symptomatic myelocytosis which is not myelocytic leukæmia. For although the myelocyte does not exist in healthy blood, it is found to a slight degree in many severe grades of anæmia, as well as in some very serious cases of infectious diseases, such as pneumonia, diphtheria, &c.

Each of the two main types of leukæmia may occur as an acute or as a chronic disease. The rarest form of all is acute myelogenous leukæmia, and the commonest form is

chronic myelogenous leukæmia. Between these extremes come, in order of frequency, chronic and acute lymphatic leukæmia. In both forms of myelocythæmia the chief cell present is the myelocyte, finely or coarsely granular. In acute lymphocythæmia it is the large lymphocyte, and in chronic lymphocythæmia it is the small lymphocyte, that dominates the blood picture. The degree to which these particular cells are present varies much; the highest figures are seen in the chronic forms of the disease, and the highest of all occur in chronic lymphocythæmia. Not only does the total number of cells attain the highest figure in this type, but the increase is apt to be purer in this type than in the others. In a patient under the writer's care, the total number of lymphocytes (mostly small) was 200,000, and the percentage of lymphocytes in a total count of 1,000 white cells was 98·7.

In all cases of multiple enlargement of the lymph glands, as in all cases of enlargement of the spleen, the examination of blood films should be undertaken in addition to the blood-count, for in this way very early cases of leukæmia are sometimes discovered. On the other hand, such an investigation may serve definitely to exclude this very serious disease when, on some other clinical grounds, its existence has been suspected.

## DISEASES OF THE LUNGS AND PLEURA

The direct pathological investigations concerned with this group of diseases fall under three heads :—

(i) Examination of the sputum.

(ii) Examination of fluid obtained by puncture of the pleural sac.

(iii) Examination of material obtained by puncture of the lung.

# CHAPTER V

## THE SPUTUM

THE word sputum is generally used in a broad sense, to include any material spat out by the patient, whether derived from the mouth, fauces, naso-pharynx, larynx, trachea, bronchi, lungs, or even from some adjacent situation between which and these organs there is an abnormal connexion. Thus, the material may come from the gums or teeth, from a peri-tonsillar or post-pharyngeal abscess, from an abscess in the lung, from an empyema that has ruptured into the lung, or from a liver abscess that has perforated the diaphragm and pleura. It must therefore first of all be determined whence the material comes, a consideration which includes a general review of the symptoms and signs presented by the patient as well as an examination of the material itself. Not all that is spat up is of pulmonary origin: there may be exspuition without expectoration. Reference will be made in chapter ix to the significance of various materials derived from the mouth and pharynx. In this section attention will be given to material which is expectorated, that is, which comes from the larynx or some part lower than this in the respiratory tract.

If, as is the case, the examination of sputum yields valuable evidence as to the nature and seat of the disease process, it follows that every assistance must be given to a patient suffering from some pulmonary disease to produce sputum, and strict injunctions must also be given to the

nurse to save it for examination. It frequently happens, and more frequently in chronic than in acute disorders of the lung, that either from habit or from motives of delicacy, sputum, though coughed up, is not spat out but swallowed: there is expectoration without exspuition. By tactful management on the part of the doctor or nurse the habit must be checked or the sensitiveness must be overruled; the provision of a sputum-pot often favours the appearance of sputum which it is alleged is not present. If the question is merely one of a tuberculous infection, the vessel may contain a little dilute carbolic acid, the presence of which does not militate against the discovery of the bacillus, but actually assists this. If, however, the material is to be utilized for purposes of culture, no antiseptic should be added, and the vessel and its cover should be sterilized by rinsing well with boiling water. Very young children do not spit up the material they expectorate, though this statement is not invariably true. Young children sometimes vomit during acute and chronic lung diseases, and when this is so, the material is often seen to contain considerable quantities of sputum, which may be isolated and submitted to examination. In the process of examination it is an advantage to pour the sputum into a flat glass dish (a large Petrie dish answers well), which is then placed on a black background. A hand lens is of great assistance in the examination. The points to be made out in the investigation of sputum are most conveniently dealt with under the particular situations whence the material is derived.

1. *The Larynx.* The actual amount of sputum which may be yielded by a diseased state of the larynx is often underestimated. Either of the three chief chronic forms of laryngeal disease—*tuberculosis*, *syphilis*, and *new growth*—when ulceration has taken place, may lead to several ounces

of sputum in the twenty-four hours. This is largely due to the ease with which secondary pyogenetic infection can occur at this situation. The sputum is usually more or less free from admixed air—i.e. is not frothy—unless there be much associated bronchitis. It is highly purulent, and, in the case of *malignant disease* especially, it is apt to contain a varying amount of blood, often bright in colour and scarcely mixed with the muco-pus. The blood may occasionally amount to a frank hæmoptysis. The microscope may reveal groups of cells suggestive, or even pathognomonic, of new growth. In *tuberculous ulceration* it is generally impossible to say how much of the sputum is contributed by the lung disease which is usually also present. And the isolation of the tubercle bacillus, even if there be no certain physical signs of disease in the lung, must not be taken to mean that the tuberculosis is confined to the larynx.

When either of these three diseases of the larynx is present in the pre-ulcerous stage, and in the condition of simple *laryngitis*, whether acute or chronic, the amount of sputum is quite small, and comparatively non-purulent. It consists for the most part of small plugs of tough mucus, usually translucent, not seldom blackened by particles of carbon if the patient is a town dweller. Needless to say, the character of the cough necessary to produce the sputum is an important indication of its place of origin. In *laryngeal* or *tracheal diphtheria*, pieces of membrane may be coughed up.

2. *The Trachea.* The sputum in tracheitis is similar in appearance to that of laryngitis. In acute cases, during the first two or three days of the disease, the bacteria of the secretion include *M. catarrhalis*, *B. influenzæ*, and the pneumococcus. As the disease progresses the flora becomes more varied, chiefly by the addition of short streptococci, staphylococci, *B. septus* (a diphtheroid bacillus),

and *M. tetragenus.* An *aneurysm* which is leaking into the trachea or left bronchus may lead to blood-stained sputum for several days, or even weeks, before the final rupture occurs. An *œsophageal fistula* may be suspected if, with appropriate symptoms, the sputum appears intimately mixed with food particles.

3. *The Bronchi.* Sputum derived from the bronchial tract, with the exception of the very small tubes (bronchioles) and sacculated dilatations (bronchiectases), is characterized by its intimate admixture with air ; the frothiness of sputum is its great feature in *bronchitis.* Conversely, the occurrence of frothy sputum indicates the presence of bronchitis, whatever other morbid condition may also be present in the lungs or pleuræ. In the early stage of *acute bronchitis* the quantity of sputum is slight—there may even be none—and the mucous element predominates. Later in the attack, and in *chronic bronchitis*, the mucus is mixed with pus, or pus may predominate. The character of the cells also varies with these stages in the disease : at first they are chiefly swollen epithelioid cells (' catarrhal ' cells) with a few polymorphous leucocytes ; later they consist more largely of the same leucocytes with fewer, and more degenerate, epithelioid elements. In some cases of acute bronchitis the cytological examination reveals large numbers of eosinophil leucocytes, as seen in asthmatic sputum. In acute bronchitis the commonest micro-organisms found in the secretion are those demonstrable in acute tracheitis ; in the chronic disease the varieties of microbes present are exceedingly numerous, so much so that it is often extremely difficult to judge which are ' pathogenic ' and which are ' saprophytic '.

There is an unusual form of bronchitis termed *pituitous catarrh,* in which the amount of sputum is apt to be very

large and rapidly formed, leading to danger of suffocation. It consists chiefly of thin fluid like gum-water, on which there is usually a layer of frothy mucus. It is not unlike the so-called 'albuminous expectoration' which occasionally follows paracentesis thoracis, but it may be very easily shown not to contain much albumin. The condition of pituitous catarrh may occur with œdema of the lung or with tuberculosis. Dr. Gee draws attention to the concurrence of this form of catarrh also with the congestion which is consequent upon a dilated heart or contracting cancer.

The sputum of bronchitis may be *fœtid*, thus giving this name to a special variety of the disease. Although the very presence of fœtor naturally raises a suspicion of gangrene or other form of lung destruction, no such condition may in reality be present; the smell is in these cases, as Dr. Gee points out, probably due to decomposition of the secretions. Anaërobic microbes can usually be demonstrated in such sputum, but their isolation rarely leads to any further knowledge as to the nature of the disease or its treatment.

In *plastic* or *fibrinous bronchitis* the sputum contains casts of the smaller bronchi and their ramifications. Care must be taken to distinguish these fibrinous coagula from *diphtheritic membrane*, which may be similarly branched when coming from some part of the bronchial tree. In all cases where casts are coughed up, in addition to the usual naked-eye and microscopic examination, cultures should be taken, because the operation of a specific micro-organism, whether that of diphtheria or not, is always an important consideration.

In *bronchiectasis* both the manner of production of the sputum by the patient, and its characters, are important points in the diagnosis. It must not, however, be supposed that all patients who cough up a large quantity of offensive

purulent material in the early morning, or after a period of quiescence during the day, are the subjects of bronchiectasis. A similar state of things may obtain in phthisis, and in chronic bronchitis with emphysema. These two morbid conditions, however, can usually be distinguished from bronchiectasis without much difficulty. The great difficulty lies in distinguishing cases of fusiform dilatation of a set of bronchi from one or more sacculated dilatations. Careful attention to the physical signs is in this matter of greater importance than examination of the sputum, which may present exactly similar features in both cases. The sputum is sometimes, though by no means always, fœtid. It may possess a distinct taste for the patient. If allowed to settle in a urine glass it generally forms into three layers. The lowest and most considerable layer consists of pus, bacteria, albuminous débris, with the occasional addition of blood and crystals. The intermediate layer is a serous fluid. The upper layer consists of muco-pus. The blood may at times be considerable in amount; indeed, hæmoptysis is a not infrequent complication of bronchiectasis, and may even be fatal. The flora is in most cases exceedingly varied, and the quantitative microbic content of the material is very high. In an investigation of the sputum bacteriologically very little is learnt by cultures made direct on to various media. (An attempt to judge the relative incidence of certain microbes by examination of a stained film made from the pus is not worth the time spent upon it.) The pus must be reduced to known dilutions, and a series of cultures made from these. Some knowledge of the bacterial content, and of the dominant micro-organisms present, can then be gained, so that in the event of vaccine treatment being employed, some confidence can be placed in the method of examination adopted.

4. *The Bronchioles.* Whatever view be taken of the essential nature of the asthmatic paroxysm, it is generally agreed that the seat of production of the peculiar sputum which often characterizes an attack is the bronchioles. Omitting the secretion which is sometimes due to an attendant bronchitis, the sputum in *asthma* is of two kinds : (i) it may be copious, very easily and quickly expectorated, and consisting of gelatinous-looking material somewhat like boiled sago, with little or no admixed air ; or (ii) it may be scanty, expectorated with much difficulty, and consist of long, slender, semi-opaque strings or spirals of tough mucin, or of similar threads curled up tightly into the so-called ' perles '. Both of these forms of sputum may concur, but more often they are seen in different patients, or in the same patient at different times. If in the same patient at different times he may speak of the attack as a ' wet ' or a ' dry ' attack, according to the nature of the secretion and his own sensations whilst expectorating it. In the condition of paroxysmal cough which often precedes true asthma, the bout may be followed after a short interval by the effortless expectoration, within a few minutes, of two or three ounces of the jelly-like mucus. As already stated, it is probable that both forms of secretion originate in the smallest bronchi, the perles being casts of these same tubes. Microscopic examination of either variety of asthmatic sputum often shows a very high percentage of eosinophil cells, a feature which distinguishes the material from the sputum of bronchitis and pneumonia. There are also present, in many samples, Charcot-Leyden crystals. The writer has recently seen numerous crystals of uric acid in a specimen, a suggestive observation in the light of the affinity which asthma has with gout. On the strength of this observation the effect of certain reputed uric-acid solvents was tried upon the patient who had

produced the sputum, but to no purpose. The bacterial content of asthmatic sputum is very low when compared with that of (say) acute bronchitis. This fact is significant in view of the recent claims of vaccine-therapists in asthma. It may be that such success as vaccine-therapy has achieved in this direction is due to the concurrence of certain infective processes of a microbic nature in the cases dealt with. Dr. Mervyn Gordon found that from a series of dilutions in two specimens of asthmatic sputum with which the writer provided him he was unable to cultivate micro-organisms from dilutions higher than 1 : 10,000 and 1 : 15,000 respectively. In two specimens of sputum from cases of bronchitis, cultures were positive when made from dilutions as high as 1 : 100,000 and 1 : 200,000 respectively. In the two asthmatic specimens the dominant micro-organisms were streptococci in both cases, of the type *S. salivarius*.

5. *The Lung.* Sputum derived from the lung varies in its characters according as the tissue is, or is not, ulcerated or destroyed by the disease-process.

(i) *Non-destructive processes.* The commonest of these is pneumonia. Pneumonic sputum is usually termed 'rusty', its colour being due to the presence of altered blood. This colour sometimes changes to a saffron tint as the disease progresses. Actual blood is not uncommon at the beginning of the disease; indeed, a pneumonia may be ushered in by a definite hæmoptysis, especially if the patient be the subject of such a condition as mitral stenosis or regurgitation. The great tenacity of the sputum in pneumonia is as significant as is its colour. If the disease be suspected the sputum must be watched very carefully, seeing that the secretion characteristic of inflammation of the alveoli may consist of a few lumps only, and these may be of quite evanescent duration. Microscopic examination will show

the presence of endothelial cells from the alveoli, with ingested erythrocytes and micro-organisms, these alveolar cells being actively phagocytic. So far the cause of the pneumonia will not have been revealed; this will turn upon the bacteriological examination. In most cases the pneumococcus is the dominant microbe, in others the influenza bacillus, and in a few the pneumo-bacillus (Friedlander's bacillus). Mixed infections are common, particularly if the form of the consolidation be lobular (broncho-pneumonic) rather than lobar. Just before, or after, the crisis, the pneumococci present not seldom look shrivelled, stain badly, and fail to grow in cultures. That is to say, they are dead. But this may also happen in the absence of a crisis. And even in cultures taken from hepatized lung on the post-mortem table it is not uncommon to find the cultures sterile, though films may show many pneumococci to be present; death of the infecting microbe in the diseased lung has not sufficed to save the patient's life. Such an observation warns us against giving a good prognosis if in pneumonic sputum the pneumococci are proved to be dead.

In *œdema of the lung*, if sputum be present, it is usually similar in appearance to that of pituitous catarrh. In the *albuminous expectoration* which occasionally follows paracentesis thoracis, a large quantity of material having the same appearance is spat up in a very short space of time; this condition is probably due to an acute œdema of the rapidly expanding lung.

In chronic *congestion* of the lung, such as accompanies a dilated heart, the sputum is usually blood-stained and shows swollen alveolar cells with granules of pigment when examined microscopically. If *hæmorrhagic infarction* complicates the congestion, and the infarct be expectorated, the result is rusty sputum or actual hæmoptysis.

(ii) *Destructive processes.* The most important of these is *phthisis.* In the early stages of chronic tuberculous broncho-pneumonia (pulmonary phthisis), whilst the lesion is a purely infiltrating one, there is no sputum. When the caseous areas begin to soften and ulcerate, the material thus formed usually finds its way into the nearest bronchi and is expectorated. Inflammation of these bronchi is an almost constant complication of the process, and the sputum accordingly shows the features of chronic bronchitis with the addition of caseous particles. Secondary pyogenetic infection of the ulcerated areas now occurs and pus is added to the sputum. By the time most phthisical patients present themselves for diagnosis, these three pathological processes have already taken place and material whereby to establish the nature of the disease is usually readily forthcoming. It is, however, in some such cases that the statement already referred to (p. 52), that there is no sputum, is often made, a statement which the character of the patient's cough frequently belies. In such cases it is well to provide the patient with a pocket flask into which he is encouraged to expectorate, and to draw his attention particularly to the coughing or 'hawking' which so frequently occurs whilst dressing in the morning. However unpromising the resulting material may appear to be—in these circumstances it is apt to consist largely of saliva—it should be very thoroughly shaken with a few drops of carbolic acid, aiming at a solution of about 1 : 20, and allowed to sediment; the solid parts should then be carefully searched for the tubercle bacillus. In some cases of phthisis, it is true, there may be no sputum at any time throughout the whole course of the disease. (In the acute miliary form of pulmonary tuberculosis, and in the so-called acute pneumonic phthisis, the absence of sputum is the rule rather than the exception.) The purulent element in

phthisical sputum sometimes takes the form of isolated lumps of comparatively airless, greenish material, which float upon the surface of the liquid in the sputum pot. This 'nummular' sputum, though suggestive of tuberculous cavity, is by no means diagnostic of it. In other cases of phthisis the sputum has all the appearances of bronchiectatic sputum, and this may, of course, be due to the co-existence of bronchiectasis with phthisis; but not always. In a few cases the sputum is fœtid.

Blood occurs in the sputum of phthisis very frequently; it probably owns a different significance according to the stage of the disease at which it appears. (i) The frank hæmoptysis which not infrequently ushers in the disease in an apparently healthy young adult—the hæmoptysis which is too often put down to 'the rupture of a small vessel in the throat'—probably indicates the relief of congestion around the infiltrating focus in the lung. Cough may be slight or even quite absent ('fluor sanguinis'), and on this account it is sometimes thought that the lung cannot be the source of the bleeding. Moreover, if the patient does own to any slight malaise before the hæmorrhage, the improvement in his condition which often follows it tends to lend support to the notion that the cause was something quite trivial. (ii) During the ulcerating stage of the disease, blood occurs in the sputum in three forms; separate lumps of frothy mucus may be brightly tinged with it, or the muco-pus may contain threads of bright or dark-red blood, as though a red strand were lying in a skein of otherwise colourless wool, or the whole of the sputum may be of a pale red colour, not unlike the colour of diluted anchovy sauce. It is likely that all these forms of bleeding result from slow or rapid oozing from the vascular wall of the phthisical cavity. (iii) When the disease is well established, large

hæmorrhages may occur now and again from ulceration of a good-sized vessel lying in the wall of the cavity. If the hæmoptysis is quickly fatal there is a high degree of probability that it is due to the rupture of an aneurysm on a branch of the pulmonary artery—a state of things often confirmed at the post-mortem examination.

Patients who have suffered for a long time from pulmonary tuberculosis which has undergone retrogressive changes sometimes cough up particles of calcareous material. This may occur some years after the disease has become quiescent ('arrested' phthisis). The passage of the calcified matter through the lung and bronchial tract may be accompanied by hæmoptysis.

The only trustworthy sign of destruction of lung tissue, other than by a process of gangrene, is the occurrence of elastic fibres in the sputum. These are not looked for as frequently as their importance deserves. In phthisis their significance has of late years been largely disregarded on account of the recognized value of the search for the tubercle bacillus. And the value of this search cannot be overestimated.

In the matter of the examination of the sputum for tubercle bacilli, the frequency with which a negative result must be repeated in any particular case is directly proportionate to the probability of phthisis given by the clinical condition. *The examination must on no account be omitted because the clinical symptoms and signs seem to be conclusive in favour of phthisis.* A repeatedly negative result may at length induce the physician to ponder a diagnosis hitherto thought to be secure. The writer has twice seen cases of lymphadenoma mistaken for tuberculosis because the wasting, the hectic fever, the sweats, the signs in the lungs and, in one case, the hæmoptysis (from a bronchiectasis due to pressure of enlarged

glands), seemed to make so complete a picture that ocular demonstration of the tubercle bacillus in the sputum was not considered necessary. For similar reasons, actinomycosis of the lung has been overlooked, and also the rare disease, pulmonary aspergillosis. It is not that the bacillus can always be demonstrated in cases of phthisis—in a small number of cases it cannot—it is rather that, in the absence of such demonstration in cases thought for clinical reasons to be tuberculous in nature, other causes of the condition must be fully considered. There is one cytological evidence afforded by sputum in favour of phthisis, and that is the presence of considerable numbers of round cells, having single nuclei, and resembling lymphocytes.

Fuller attention is now being paid to the secondary microbic infections in phthisis than was formerly the case. These pyogenetic infections of phthisical cavities and of the inflamed bronchi in phthisical lungs are known to be accountable for many of the symptoms in the later stages of the disease. Indeed it is probable that in not a few cases the pyogenetic cocci are of more importance than the tubercle bacillus. Hence the need for increased knowledge of the pyogenetic flora present in these cases. But, as noted in the paragraph dealing with bronchiectatic sputum, so in phthisical sputum, it is of paramount importance to undertake quantitative estimations of the bacterial content if any good is to be expected from vaccine or other specific therapy in this connexion. In each of two cases in which the writer adopted the method of decimal dilutions, the micro-organism present in greatest abundance was a streptococcus of the salivary type; staphylococci were present in a very much smaller degree.

*Gangrene of the lung* is made manifest by the expectoration of sputum of a characteristic odour in which are found pieces

of lung tissue preserving more or less its histological structure, or elastic fibres in an isolated condition. The sputum sometimes separates into three layers as in bronchiectasis.

In *abscess of the lung* the distinction from gangrene, so far as the sputum is concerned, turns upon the absence of the gangrenous odour and the absence of pieces of intact lung tissue. The sputum is usually very fœtid, as is the breath also; in one case under the writer's care the odour of the breath was exceedingly putrid whilst that of the sputum was not so. Isolated elastic fibres occur in the sputum of abscess as of gangrene.

*Actinomycosis of the lung* depends very largely for its diagnosis upon sputum examination. The granules of the fungus, yellowish in colour as a rule, but occasionally black, may be seen with the naked eye or with a hand lens. Any suspicious particles of this kind should be isolated, and examined microscopically. By the time the ray-fungus is expectorated secondary pyogenetic infection of the granulomatous focus has occurred, leading to free purulent sputum.

*Hydatid disease* shows itself occasionally by the appearance of hooklets and scolices during microscopic examination of the sputum, less often by the expectoration of pieces of the daughter cysts.

The sputum in *malignant disease* of the lung is usually said to resemble prune-juice, from the admixture of much altered blood. Quite as often, however, it consists of fairly copious muco-pus, which may be fœtid. Microscopic examination may (rarely) reveal the histological features of cell-nests or of sarcomatous tissue. In some cases there is copious expectoration of material similar to that of pituitous catarrh.

6. *The pleura.* Sputum of some sort is often present in

*pleurisy* and is usually of the muco-purulent variety. If an effusion collects rapidly more or less blood may be present also. In both of these conditions the material comes, not from the pleura, but from the subjacent lung and bronchi.

In a few cases of pleurisy with effusion the sputum, or the greater part of it, may come from the pleura itself: the liquid which has collected in the sac ulcerates through the membrane into the lung and so is expectorated:—

(i) An *empyema* is not infrequently 'coughed up' in this manner ('phthöe'), leading to the sudden expectoration of a quantity of pus. In the majority of such cases the patient has been ill immediately prior to the event, though physical signs of the empyema may not have been discovered. It occasionally happens, however, that the sudden pyorrhœa is the first evidence of anything amiss. In one such case a gentleman, whilst riding, was alarmed by a violent fit of coughing which resulted in partial suffocation by a quantity of pus. The cough passed off completely, but the incident was repeated some three months later. The origin of the empyema was probably a fractured rib sustained several months before the cough occurred. In this case bronchiectasis resulted as a sequel to the condition—a state of things not unusual in this mode of spontaneous drainage of an empyema. In the purulent sputum obtained for examination nine months later the pneumococcus was found to be the dominant micro-organism.

(ii) Very rarely a *serous pleural effusion*, behaving in a similar manner, makes its way into the lung and is expectorated. This has probably been recorded in two instances only.

7. *Parts adjacent to the lung.* Certain situations near to the lung and pleura may be the source of the sputum.

A *liver abscess* may extend through the diaphragm and pleura, and its contents may be expectorated. The material has at first an appearance like anchovy sauce; later it may be less coloured. The microscope may reveal amœbæ. Bile-pigments and bile-salts may be shown to be present by chemical tests. Fragments of tissue having the histological features of liver cells may also be demonstrated. In rare cases crystals of leucin and tyrosin have been found.

Both actinomycosis and hydatid disease of the lung may be secondary to a primary focus in the liver.

# CHAPTER VI

## PLEURAL PUNCTURE

### I. GENERAL

PUNCTURE of the pleural sac with a clean, sharp, hollow needle is indicated in every case when there is a suspicion of a pleural effusion, however small. Certainly it is indicated in every such case when the primary disease is located in the pleura or lung; in some cases of chronic valvular disease with anasarca no special knowledge is likely to be gained by the puncture. It should not be thought unnecessary because the suspected effusion is very small, and causing no discomfort to the patient; the writer is here considering, not the treatment of the disease by removal of the fluid, but the diagnosis of the disease and of its cause. The first object of the puncture is to demonstrate that fluid is, or is not, present; the second object is to obtain a specimen of the fluid, if present, for examination. These aims are of such vital importance to the patient himself that any consideration of slight distress incurred by the puncture should be met by a straightforward explanation from the practitioner. The physical distress may be minimized by using a needle that is sharp and clean. Nothing is better than a small glass syringe with needle attached; the use of a trocar and canula, especially the ill-fitting sort which has a shoulder where the trocar emerges, is to be deprecated; this form of instrument may often be seen to push the skin before it and to burst through the

chest wall rather than pierce it—a procedure not calculated to increase the confidence of a patient who has been told that his chest is merely to be pricked. As to the mental distress, this is too often increased by the elaborate preparations frequently made to guard against sepsis—preparations which include vigorous scrubbing of the patient's skin with a nail-brush, the copious application of lotions, and the attendant exposure of the greater part of the patient's back. In point of fact puncture of the chest wall is too often 'an operation' instead of a simple and almost painless method of clinical examination.

Of the value of the puncture as a means of proving the mere presence of fluid, little will be said here: this is purely a question of clinical medicine. It suffices to say that the physical signs of pleural effusion are notoriously deceptive, and may be so equivocal that to reason concerning them is waste of time. Moreover, a dry puncture needs never be a matter for shame, whereas the discovery of an undiagnosed pleural effusion late in the course of the disease, or after death, is certain to cause regret. The writer is here concerned with the value attaching to the examination of the fluid itself, and the help in diagnosis and treatment thus afforded.

## II. MODE OF MAKING THE PUNCTURE

The patient, suspected of a pleural effusion, is already in bed. Unless he be acutely ill the best position is the sitting one, with head bent forwards and hands placed on the knees, thus rotating the scapulæ into a favourable position. If acutely ill the position of the patient is semi-prone, the affected side being uppermost. A couple of pillows are placed beneath the unaffected side. The arm of the affected

side is brought well to the front. But it occasionally happens that the puncture is to be made in the front of the chest, as when an empyema is suspected at the apex of the lung. In this case the patient lies on his back, with a pillow beneath the shoulders and the head turned to the unaffected side. While the glass syringe and needle are being boiled the skin immediately over the seat of puncture is treated first with soap and water and then with alcohol, ether, or acetone, using pads of cotton-wool for the purpose. If an empyema be suspected the needle must not be too fine, lest it meet with pus too thick to flow along it. For an adult the needle should be at least three inches long, and stoutly made, so that it does not bend easily. It should not be necessary to support the needle near the point by the index finger as it is being pushed through the chest wall. The place of puncture is determined almost solely by the physical signs: the puncture is made where the signs of effusion are most marked. Somewhere near the angle of the scapula is the point of election in most cases of pleural effusion. In very small effusions, or in cases presenting physical signs in unusual situations, some discretion may be necessary to avoid wounding the heart, the big vessels, and the diaphragm. The costal interspace, and the point in it, having been chosen, the needle is inserted immediately above the lower rib and is held at right angles to the skin. These two cautions are observed in order to avoid wounding the intercostal artery—a very rare accident, yet one which the writer has observed upon a single occasion. The chest wall is now quickly pierced. When, by gentle suction, the syringe has been filled by the fluid, or the puncture has been proved to be 'dry', the needle is quickly removed. The drag of a needle upon the skin during withdrawal is painful; the skin is therefore prevented from

following the needle by pressure of the finger close to the point of insertion. When puncture of the chest is performed in this manner, it is not a painful process, and it is often possible to repeat it once or twice at the same examination without causing any distress to the patient. It is customary to seal the puncture with a small piece of gauze or wool soaked in collodion.

### III. NAKED-EYE EXAMINATION OF THE FLUID

The puncture at once determines the nature of the effusion, whether serous, sero-purulent, hæmorrhagic, milky or chalky. So that already there is presumptive evidence in favour of certain causes of the effusion.

(i) A *serous effusion* is most often due to tuberculosis of the pleura. It sometimes complicates rheumatic fever, is less often due to the pneumococcus, and is rarely associated with a streptococcal infection. If the fluid quickly coagulates into a firm jelly this indicates abundant fibrin formation and an inflammatory origin of the effusion. If clotting is partial, or almost absent, it is likely that the fluid is more a passive transudate than an inflammatory exudate. A small serous effusion may co-exist with a definite septic focus, such as abscess or gangrene of the lung. If, therefore, the symptoms or signs, or the character of the sputum, suggest either of these conditions, caution must be exercised in the interpretation of the result of puncture.

(ii) *Sero-purulent effusion*—thin turbid fluid—is rather common as a result of pneumococcal infection. It may accompany lobar consolidation of the lung. Although it is to be classed among the purulent rather than the serous effusions, it does not usually call for immediate removal, still less for resection of a rib ; for it is frequently absorbed after

the diagnostic puncture has been made. Many cases of lobar pneumonia are associated with a small effusion of this kind. Chronic pleural effusions, or effusions which have remained unabsorbed for a long period of time, are frequently turbid, as the result of much débris of leucocytes and other molecular matter.

(iii) *Purulent effusion* (*empyema*) indicates pyogenetic infection—by pneumococcus, streptococcus, or staphylococcus, in this order of frequency. Its discovery is an indication for free drainage by means of resection of one or more ribs. But if the disease is acute, the cause pneumonia, and the patient is a child, resolution sometimes takes place after removal of the fluid by puncture alone. This result is not, however, to be anticipated. Although empyema is often regarded as a possible result of tuberculosis most authorities are agreed that this is a rare event, if, indeed, it occurs at all. It may be confidently assumed that, if the patient be tuberculous, the infection is a mixed one, and that pyogenetic micro-organisms are present as well as the tubercle bacillus.

(iv) *Hæmorrhagic effusion*, contrary to much that is taught on the subject, is most often due to the same cause as simple serous effusion, that is, to tuberculosis. Compared with this cause new growth of the pleura takes a second place as regards frequency. The effusion complicating heart disease, especially when associated with infarction of the lung, is prone to be bloody. So also is the effusion sometimes associated with aortic aneurysm. If pleural effusion occur in scarlet fever it may be hæmorrhagic. Lastly, any of the so-called hæmorrhagic diseases —purpura, hæmophilia, scurvy, leukæmia—may be complicated by blood-stained pleural effusion.

(v) *Milky effusion*. This is perhaps the best generic

name for the three different forms of opaline effusion met with. (*a*) The effusion may be *chylous*, consisting of true chyle, and due to the escape of this fluid from the thoracic duct, or from one of its tributaries, into the pleural sac. In this effusion the fat rises to the surface as a cream. (*b*) *Chyliform effusion* is not to be distinguished from true chylous effusion by the naked eye, but it has much less tendency to 'cream'. (*c*) *Milky non-fatty* effusion does not cream at all. Neither (*b*) nor (*c*) indicates a lesion of the thoracic duct system; little is known, however, of their origin.

(vi) *Chalky effusion* is white and opaque, due to the presence of calcium phosphate. It does not appear to be proved that this condition is due to the escape of material from a softened calcified gland into the pleura, although calcified bronchial glands have been found in such a case post mortem.

### IV. THE CHEMISTRY OF PLEURAL EFFUSION

The specific gravity of serous effusions is usually that of normal urine, 1015–25; a low specific gravity (e.g. 1006) indicates that the fluid approximates to the nature of a hydrothorax, as in heart disease. The quantity of protein present varies directly with the inflammatory nature of the exudate—it may be as high as 4–5 per cent. The presence of Bence Jones protein (hetero-albumose), a rare event, signifies myeloma, local or diffuse. The occurrence of a little sugar has no significance.

### V. THE CYTOLOGY OF PLEURAL EFFUSION

1. *Serous effusion.* It is in connexion with pleural effusions that most of the researches into the cell-content of exudates and transudates have hitherto been directed. These researches, pioneered by Widal and Ravaut, have

shown that a different cell-content is present according as the cause of the effusion is inflammatory or transudatory; and again, in the inflammatory effusions, according as the cause is tuberculosis or pyogenetic infection. Widal and Ravaut, as the result of their observations on pleuritic serous effusions, enunciated the following cytological formula:—*When the dominant cells present in a pleural effusion are small lymphocytes the probable cause of the inflammation is the tubercle bacillus; when the dominant cells are polymorphonuclear leucocytes the probable cause is some pyogenetic micro-organism.* During the early stages of a tuberculous pleurisy the predominance of the lymphocyte is less marked than as the effusion progresses; the polymorphous cells may even be in excess during the first three days of the effusion. Sufficient confirmation of this formula has now been advanced to make the routine cytological examination of all pleural effusions a valuable aid to diagnosis. In the secondary pyogenetic infection which not uncommonly complicates tuberculous pleurisy when phthisis is present, a gradually increasing number of polymorphous cells appear in the exudate, thus disturbing the proportions seen in primary tuberculous pleurisy.

In *rheumatic pleurisy*, which occasionally goes on to liquid effusion, the presence of isolated endothelial cells is a marked feature of the cytological examination.

In *pleural transudates*, such as accompany heart and kidney disease, endothelial cells are again a striking feature. Dr. Emery draws attention to the fact that whereas in rheumatic and some other pleuritic effusions the endothelial cells are highly phagocytic, this character is not seen to any marked degree in passive exudates. Here the endothelial cells are often seen in mosaic, or, as it has been termed, in 'placards'.

In pleural effusion complicating suspected *malignant disease* of the lung or covering membrane the fluid should be carefully searched for histological evidences of new growth. It must be confessed, however, that the difficulty of distinguishing between groups of endothelial cells and cells derived from an ulcerating tumour is very great. Even the presence of mitosis, as Dr. Emery points out, does no more than suggest malignancy.

*Eosinophilia* in a pleural exudate is an uncommon event and one which at present has no positive diagnostic significance. But inasmuch as in none of six recorded cases was any evidence of tuberculosis forthcoming, the occurrence of eosinophil cells in an effusion is probably a fact pointing against this form of infection.

11. *Empyema.* The occurrence of pus is but an extended degree of dominance of the polymorphous cell in the exudate, with the significance already observed (p. 74).

## VI. THE BACTERIOLOGY OF PLEURAL EFFUSION

The search for micro-organisms must be conducted by film preparations, by culture, and (if necessary) by animal inoculation.

1. *Serous effusion.*

(i) In most cases of serous pleurisy no micro-organisms are demonstrable by either of the first two of these methods. Out of forty-nine consecutive cases examined bacteriologically at St. Bartholomew's Hospital the writer finds that forty were sterile on cultivation (over 80 per cent). The reason of this is that most cases of serous pleurisy are *tuberculous* in origin. This fact was suspected long before the tubercle bacillus was discovered. Although a few authorities still contest this view, the majority accept the conclusion as substantially proved. Cases of acute sero-fibrinous pleurisy

certainly occur in which, with the most painstaking and modern methods of investigation, the presence of the bacillus cannot be demonstrated. But in any series of such cases there is good evidence that in the majority the cause is as stated. It may be useful in this place to review in its entirety the evidence for accepting the above doctrine.

(*a*) *Post-mortem evidence.* Acute pleurisy is not a very fatal disease : the mortality is about 20 per cent. But in many of the patients who die signs of active tuberculosis are found at the necropsy. Of 131 patients thus examined Professor Osler found this to be the case in 32 (24·4 per cent). Dr. Theodore Fisher, in an analysis of 240 recent necropsies, found old pleural adhesions present in 41 ; of these 28 showed evidence of old tuberculosis of the lung.

(*b*) *Clinical evidence.* In a considerable number of the cases clinical evidence of tuberculosis is found in the lungs or in other organs. Signs of phthisis, not previously detected, are sometimes clearly manifested after paracentesis. In 195 cases of pleurisy in which the sputum was examined tubercle bacilli were found by Professor Osler to be present in 30 (15·3 per cent).

(*c*) *Presence of the bacillus in the exudate.* The demonstration is notoriously difficult, and this is so even in cases which, for other reasons, are known to be undoubtedly tuberculous. The adoption of more recent methods has given a larger proportion of positive results ; this is true both as regards the isolation of the bacillus direct from the effusion and also as regards the inoculation of guinea-pigs with the fluid. By a simple process of sedimentation and the staining of films the bacillus has been demonstrated in 55 per cent of twenty-two cases. By his method of 'inoscopy'—digesting the clot, which forms after allowing the fluid to stand, with artificial gastric juice, centrifugalizing

the deposit, and preparing films—Jousset claims to have found the bacillus in all of twenty-five cases. (Other observers, however, have not had such complete success with the method as this.) Some pathologists get good results by allowing the clot to shrink, hardening it, cutting sections of the embedded material by the paraffin method, and staining these with carbol-fuchsin. If the search for the bacillus be undertaken by inoculation of a guinea-pig, which must be regarded as by far the most critical method, the proof of tuberculosis is probably as high as 90 per cent (Le Damany produced tuberculosis in the pig as often as fifty-one times in fifty-five cases). It is important, in performing the inoculation, to use large quantities of the fluid ; at least 20 c.c. should be injected.

(*d*) *Cytodiagnosis* (see p. 74) favours the view that most cases of sero-fibrinous pleurisy are tuberculous, the cells present in the fluid being chiefly lymphocytes, often to the extent of 100 per cent in a count of 100 to 200 cells.

(*e*) *The tuberculin test* (see chap. xiii) gives a positive reaction in pleuritic patients in about three-quarters of the cases (Lord found 76·5 per cent, and Beck 73·7, of positive results). There is here, however, the fallacy that the reaction may be due to a tuberculous focus elsewhere in the body than in the pleura.

(*f*) *The subsequent history* of the patients supports the same conclusion. A large number of them suffer afterwards from tuberculous disease, and especially from pulmonary phthisis. Bowditch was the first to adduce figures in this connexion : of 90 cases traced during the thirty years 1849–79, 32 died of phthisis. Dr. Hedges followed up 130 cases of pleurisy treated at St. Bartholomew's Hospital and found that 40 per cent of these had become tuberculous within seven years. Of 300 cases from the Massachusetts

General Hospital, investigated by R. C. Cabot, 117 were found to have died within five years.

(*g*) *The evidence of inheritance* may also be adduced: many of the patients belong to tuberculous families, and have inherited a tendency to the disease. Occasionally it is seen that phthisis is preceded by sero-fibrinous pleurisy in parent and in son or daughter, the same sequence being closely followed in both generations.

(ii) As already mentioned, a serous effusion is sometimes *pneumococcal* in origin. This may be so whether there is concurrent hepatization or not. But usually there is concurrent hepatization. The pneumococcus is found without difficulty, and often in the films as well as by culture. In cases in which there is no consolidation of the lung, or other complication, the discovery of the pneumococcus in the fluid is a good prognostic sign, much better than if the fluid yield no micro-organism on culture. And even if a serous pneumococcal effusion become purulent the prognosis, as stated below, is not usually serious.

(iii) Occasionally a serous pleuritic effusion is due to a *streptococcus*. In studying some 200 cases of streptococcal infection Dr. Andrewes and the writer met with two instances, and Dr. Mervyn Gordon has investigated one. In all three cases the streptococcus was a variant of *S. pyogenes*. In the post-mortem room it is not rare to find streptococci in the pleural exudate accompanying rheumatic fever.

(iv) The *typhoid bacillus* is a rare cause of pleuritic effusion. According to T. M'Crae's figures pleurisy occurs in only 0·2 per cent of cases of typhoid fever (3 cases in 1,500). Nevertheless, pure cultures of the bacillus have from time to time been obtained from the pleuritic fluid. In one instance the effusion was hæmorrhagic. Pleurisy during convalescence from typhoid fever must not be confounded

with pleurisy during the fever. Post-typhoidal pleurisy must be regarded with the utmost suspicion, for it is very prone to be the work of the tubercle bacillus. Even if the typhoid bacillus be isolated from a case of pleurisy, tuberculosis must none the less be suspected: inoculation of a guinea-pig has, in these circumstances, proved the presence of the tubercle bacillus.

(v) *Pfeiffer's bacillus* (*B. influenzæ*) has been isolated from pleuritic effusion in a few instances. So also has the *gonococcus*.

2. *Empyema.*

In the great majority of cases of purulent pleural effusion micro-organisms are isolated without much difficulty. Indeed, the proportion of cases yielding positive results on culture media to those proving sterile is almost exactly the reverse of that found with serous effusions; in empyema 80 per cent of cases give a growth of bacteria.

(i) The *pneumococcus* is considerably commoner than any other microbe; the author found the frequency to be 75 per cent in 32 consecutive cases examined at St. Bartholomew's. Fralcy found it to be 52 per cent at the Pennsylvania Hospital, and Lord found it to be 40 per cent at Massachusetts. In Netter's series of 109 cases the pneumococcus was present in 53 per cent. Reference has already been made to the comparative benignancy of the cases when this micro-organism is reported as being present. In the empyema of childhood it is probable that the frequency of the pneumococcus is considerably greater than is shown by the above figures, which include all ages.

(ii) Next in frequency is the *streptococcus*, relatively more common in the empyema of adults than of children. Netter gives the frequency of streptococcus as 46 per cent—a

much higher figure than that obtained by English and American workers. Lord's figure is 20 per cent, Fraley's is 21 per cent, and the writer's is 20 per cent. It may be concluded that the pneumococcus accounts for nearly three-quarters, and the streptococcus for nearly one-quarter, of all empyemata. Dr. Andrewes and the writer found the type of streptococcus to be most often *S. pyogenes.*

(iii) Of the remaining cases of empyema (less than one-quarter) the *staphylococcus* accounts for a few, probably less than 5 per cent. If empyema complicate osteomyelitis this is the micro-organism usually present, the type being *S. aureus.* Mixed infection, either with the tubercle bacillus or streptococcus, is not uncommon, if the staphylococcus be present, and if the case is not one of staphylococcal pyæmia.

(iv) The *tubercle bacillus*, according to most English pathologists, is rarely if ever the sole cause of empyema.

Netter's figure for tuberculous empyema (11 per cent) is certainly not the experience of most observers, if mixed infections be disregarded (*vide* p. 72).

(v) *B. typhosus, B. coli, Pfeiffer's bacillus, actinomyces.* These micro-organisms have all been found in empyema, perhaps as often in mixed infection as in pure culture. A not uncommon combination is actinomyces with staphylococci—a combination which usually gives the pathologist considerable difficulty in obtaining pure cultures of the separate germs.

The presence of diphtheroid micro-organisms is often reported. But it must be remembered that these are common contaminations of the skin and of certain sinuses. On this account their presence in pus sent for examination probably has little pathological significance.

## VII. TOXICITY OF PLEURAL EXUDATES

Quite apart from the action of any bacteria contained in the fluid, there is evidence that pleural effusions possess toxic properties. Very few observations, however, have been made on this point and practically no animal experiments. The writer has more than once observed the rapid absorption of the fluid in a patient to be associated with fever, and on this account a higher range of the temperature occurring at any stage of the disease need not be regarded as of bad import provided the physical signs indicate diminution of the effusion. An Italian physician has attributed convulsions in a patient to the rapid absorption of a pleural effusion. It has been found that the hypodermic injection of 1 c.c. of his own pleuritic exudate into a patient who had been proved to be tuberculous produced a general reaction similar to that seen in a positive tuberculin reaction. It has therefore been suggested that this procedure may possibly differentiate the tuberculous from the non-tuberculous cases. In one case in which the writer twice inoculated a patient with his own pleural fluid no sort of reaction occurred; nor did the injections appear to influence the rate of absorption of the effusion. This case was not demonstrated with certainty to be tuberculous, although it probably was of this nature. Further observations along these lines seem worthy the making.

# CHAPTER VII

## LUNG PUNCTURE

### I. GENERAL

PUNCTURE of the pleura has long been practised as a valuable aid to diagnosis. For many years before the birth of bacteriology the procedure yielded important knowledge. But prior to the advent of the histologist and the bacteriologist a 'dry' puncture of the chest wall was wholly negative in its information. The needle either entered a pleural effusion or it entered the lung. If the latter, the very small amount of blood-stained fluid which was brought away by the syringe was neglected. And even to-day this valuable material is usually discarded without examination. As a matter of fact, these few drops of lung juice may yield very important positive information as to the presence of disease within the lung itself, and also as to the nature of such disease. During the past four or five years the writer has now and again employed this method of investigation with extremely useful and interesting results. It has been thought well to collect such observations as have been made with regard to it.

In actual practice a diagnostic puncture of the lung may be made under two conditions: (1) a pleural effusion is suspected and the result of the puncture negatives this; or (2) no fluid is suspected in the pleural sac, but the lung is deliberately punctured for the express purpose of discovering the nature of a disease process within the lung itself. The material obtained is no less valuable in the first than in the second of these two conditions.

## II. INDICATIONS

Puncture of the lung is indicated : (1) In any case yielding signs of consolidation of the lung, in which careful examination of the sputum fails to reveal the nature of the disease, and in which satisfactory progress is not being made. It is, perhaps, pushing the value of 'ocular demonstration' rather far to say that lung puncture is indicated in a straightforward case of lobar pneumonia, even when there is no sputum for examination. But it should certainly be undertaken in any such case if the desired clinical course is departed from in any way to the prejudice of the patient. The puncture will frequently reveal the existence of a mixed infection (e.g. *B. influenzæ* and *pneumococcus*) when this is not suspected. Two other indications exist. (2) In abscess it is useful to obtain a specimen of pus from the actual seat of suppuration, for thereby a more accurate knowledge of the causal microbe is gained than is possible when dealing with the sputum. (3) In bronchiectasis the same comment holds ; the flora of the sputum is notoriously varied and difficult of interpretation.

## III. TECHNIQUE

The mode of performing the puncture follows exactly that of exploration of the pleura. For obvious reasons it is advisable to use a good-sized needle. Provided this be quite clean and sharp the patient suffers very little discomfort. And if due regard be had to the anatomy of the heart, big vessels, and diaphragm, no damage is at all likely to occur. It should be noted that no risk is run which is not present with every negative pleural puncture,

and this latter proceeding is notoriously free from danger when carefully undertaken. The syringe, of course, has been recently boiled and contains no disinfectant. The puncture is made at a point on the surface of the chest immediately over an area of lung yielding abnormal physical signs. The needle is inserted into the lung, the piston is withdrawn about an inch so as to keep up a gentle suction, and the needle is then slowly removed whilst the skin is supported by the finger and thumb of the left hand. As the needle leaves the chest wall two or three drops of bloody fluid are seen to spurt from it into the barrel of the syringe.

The method of dealing with the material depends somewhat upon the amount obtained. Sometimes the amount is so small that it is advisable to utilize the whole of it for purposes of cultivation of micro-organisms, the method resolving itself into one of 'lung culture'. If, however, the quantity admits of this, or if a cytological, rather than a bacteriological, examination is suggested from the nature of the patient's illness, films are also prepared from the material and stained as in the case of pus. In either case the needle is inserted into a little sterile salt solution, just sufficient of which is drawn up into the barrel to mix with the lung juice, and to enable this to be completely discharged. If a bacteriological examination only be decided upon the diluting fluid may well be a little sterile broth from a culture tube. The mixture of lung juice and diluting fluid is now squirted out, partly on a glass slide for film examination and partly on to the surface of an agar slope, which is incubated at 37·5° C. As the material removed from the lung is almost certain to contain a little blood, even hæmophilous microbes, such as *B. influenzæ*, need no other medium than ordinary agar. If the cultures are sterile,

the films may yet give valuable information of a cytological kind bearing upon the nature of the disease process.

## IV. ILLUSTRATIVE CASES

The following cases demonstrate the assistance in diagnosis and treatment afforded by lung puncture :—

Case 1. *Abscess of lung following perforated duodenal ulcer.*—The patient was an international football player, under the care of Mr. C. M. Hewer, of Tarporley, who diagnosed perforation of a duodenal ulcer. The perforation was sutured by Mr. G. P. Newbolt, of Liverpool. A week after the operation signs of pleurisy developed at the base of the right lung, with fever and severe illness. Percussion dullness followed at the seat of the pleurisy, but exploration of the pleura by needles was negative. When the writer saw the patient with Mr. Hewer there were marked signs of consolidation of the lung, high intermitting fever with sweats, and dilated heart. The condition of the abdomen was satisfactory. Four separate punctures with a good-sized needle failed to show fluid in the pleura. The lung juice obtained at the last puncture, however, was dealt with as above described, and on the next morning there was seen to be a copious and pure growth of streptococcus on the agar slope. On further examination the streptococcus was found to be *S. fœcalis.* Polyvalent antistreptococcus serum was given liberally, and undoubted benefit resulted. Abscess formation then took place in the lung, and large quantities of very fœtid pus were expectorated, as much as 1½ pints in the day. But the acute and alarming symptoms had passed off. Vigorous treatment in the open air, with respiratory antiseptics by the mouth and by inhalation, led to complete recovery. In this case the lung puncture was not per-

formed deliberately, but during the search for an empyema.[1] But the important information obtained from the examination of the lung juice in this instance, proving as it did the presence of a pulmonary focus of infection by streptococci derived from the bowel, led the writer to employ the method directly in other cases where there was doubt as to the nature of the disease in the lung.

CASE 2. *Abscess of lung following incomplete abortion.*—A woman, aged 30 years, came under observation fourteen days after a miscarriage, suffering from fever, rigors, anæmia, and shortness of breath. The uterus was curetted and treated with antiseptics without improvement. A week later signs of consolidation appeared at the base of the right lung in front, with local pain and cough. There was no sputum. Exploratory puncture of the lung drew off two or three drops of blood-stained pus, and these yielded a pure culture of *Staphylococcus aureus*. The signs persisted and the patient grew worse. An operation was advised, but it was considered that the indications for resection of a rib and exploration of the lung were insufficient. Death occurred a week after the puncture was made. Post-mortem examination showed an abscess situated in the right lower lobe of the lung close to the pleura. The pus from the abscess gave a pure culture of *S. aureus*.

CASE 3. *Appendicectomy ; general peritonitis ; pneumonia.* —A child, aged 5 years, was admitted to the Great Northern Central Hospital under the care of Mr. E. C. Stabb. Laparotomy revealed a gangrenous appendix, which was removed. The child did very well until the tenth day, when signs of peritonitis and pneumonia appeared. Puncture of the lung was undertaken, and a few drops of bloody fluid were

[1] This case was fully reported by Mr. Newbolt in the *Liverpool Medico-Chirurgical Journal* for January 1907.

obtained which gave a copious growth of *pneumococci*, *B. coli*, and *B. influenzæ*. The proof of the mixed infection of the lung was very striking. A dose of pneumococcus vaccine was given, but the child was obviously in a desperate condition at the time and died four days later.

CASE 4. *Mycosis fungoides; streptococcal and staphylococcal infection of the skin; extensive pneumonia.*—A man, aged 38 years, who had suffered for several years from recurring attacks of mycosis fungoides, came under observation with a large axillary abscess due to staphylococcal infection. There were also present several superficial foci of streptococcal infection on the chest and limbs. The abscess was incised, scraped, and drained. A spreading pneumonia developed, but whether this was streptococcal or staphylococcal in origin was uncertain. Lung puncture gave a little blood-stained fluid showing in films many cocci, which cultures proved to be *Staphylococcus aureus*. Two small doses of the killed staphylococcus were given as vaccine, but the condition proved to be the usual mode of termination of this uncommon skin disease.

CASE 5. *Erysipelas; broncho-pneumonia.*—An infant, aged 7 months, was admitted to the Great Northern Central Hospital under the writer's care, suffering from extensive erysipelas of the scalp. Several small superficial abscesses developed, and from these a pure culture of *Streptococcus pyogenes* was obtained. The condition improved under treatment by antistreptococcus serum. There developed later several vesicles on the scalp, and from these a growth of *S. aureus* was obtained. Patches of consolidation also appeared in the lower lobe of the right lung, and it could not be said whether these were due to staphylococcal or streptococcal infection, or to a mixed infection. Puncture of one of these areas of solid lung revealed a pure staphylococcal infection.

The infant was accordingly vaccinated, but without good effect.

CASE 6. *Delayed resolution in pneumonia ; negative lung puncture.*—A young man, aged 20 years, was admitted to the Great Northern Central Hospital under the writer's care on the second day of his illness, suffering from pneumonia, with consolidation of the right lower lobe and some associated bronchitis. A pseudo-crisis occurred on the seventh day, but the temperature rose again on the same day, and the signs of consolidation remained unchanged. On the twenty-third day the temperature was still raised, in an intermittent fashion, and the physical signs, as well as a skiagram, showed the lung to be still hepatized. The leucocyte count was 20,000. Examination of the sputum showed no tubercle bacilli. The solid lung was punctured, and the blood-stained fluid was submitted to culture. The agar tubes remained sterile. By the twenty-sixth day the temperature was normal and the general condition was excellent. Injections of fibrolysin were given ; the patient left the hospital in good health, but with the lung still solid.

## V. CONCLUSION

Altogether the writer has punctured the lung for diagnostic purposes in some sixteen cases. Those above cited serve to show the kind of information that can be elicited by this mode of examination. It may possibly be found of service in suspected cases of early and localized pulmonary tuberculosis, in which condition sputum is so commonly absent. In one such case the writer punctured the affected lung, but failed to demonstrate the tubercle bacillus in films prepared from the material obtained. In cases of acute miliary tuberculosis of the lung the bacillus can be readily

demonstrated by this method. At a time when vaccine-therapy appears to be so promising in dealing with many localized infective conditions the prompt isolation of the causal micro-organism becomes a point of paramount importance. When the affected organ is the lung the particular investigation here referred to may be the sole means of obtaining the necessary culture from which to prepare the vaccine. Quite recently Dr. J. C. Briscoe has published cases of acute and subacute pulmonary infection, treated by vaccines, in which the micro-organism was obtained directly by lung puncture. Dr. W. H. Willcox has employed the same method in certain cases of pneumonia where sputum was not available. The latter worker injects a few drops of sterile broth into the lung prior to withdrawing the lung juice. The writer is doubtful, however, if this procedure is desirable, and he has not found it necessary.

# CHAPTER VIII

## LUMBAR PUNCTURE

### I. GENERAL

SINCE the introduction of pleural puncture it is probable that no more valuable addition has been made to our methods of clinical examination than that of tapping the cerebro-spinal fluid as suggested by Quincke. It is strange to notice with what difficulty this useful diagnostic and therapeutic procedure has gained a foothold, especially in England. Six years ago it was not practised at all in some of the large teaching hospitals of London. Even to-day some physicians regard the proceeding as novel, and give but a half-hearted consent to its performance, fearing the consequences to the patient. Between this attitude of conservatism, born of an incomplete knowledge of the technique of the puncture and the value of the information gained thereby, and the unguarded zeal of those who employ the test somewhat indiscriminately on hospital out-patients, there is much room for systematic investigation carried out carefully and under proper conditions. With this last-named qualification it may be confidently asserted that the method is quite free from risks, and entails but little discomfort to the patient. The writer has never seen any ill effects follow the proceeding in over a hundred lumbar punctures which he has personally performed or supervised. In any suspected case of meningitis a lumbar puncture is as clearly indicated as is puncture of the chest in a suspected case

of pleural effusion. In view of the fact that meningitis is a much more serious disease than pleurisy with effusion, and for the reason that the physical signs of the latter disease are less equivocal than are those of the former, lumbar puncture is even a more urgent necessity in the diagnosis of meningitis than is pleural puncture in the diagnosis of pleural effusion. Of late years the introduction of spinal anæsthesia has given a fresh impetus to lumbar puncture, and has been of definite service in popularizing the procedure for diagnostic purposes.

## II. INDICATIONS

1. *Diagnostic indications.*

The conditions in which lumbar puncture becomes advisable are year by year increasing, as our knowledge of the cerebro-spinal fluid and the changes which it undergoes in disease is extended.

(i) The most important indication lies in the diagnosis of *acute meningitis*, between which and certain toxæmic states associated with headache, delirium, and fever, a differential diagnosis on purely clinical grounds may be quite impossible. A very careful clinical investigation of a case presenting this triad of symptoms, or of any set of symptoms raising a suspicion of meningitis, quite frequently results in a diagnosis that rests on probabilities only. For several of the symptoms of meningitis are by no means pathognomonic, and are occasionally seen in such cases as typhoid fever, pyæmia, pneumonia, and middle ear disease. Such are headache, delirium, vomiting, irregular pulse, absent tendon-jerks, stiffness of the neck, and Kernig's sign. Optic neuritis and various paralyses occupy, it is true, a less equivocal position in the symptomatology. But these

signs are very frequently absent in meningitis, especially in the early stages, when diagnosis is of paramount importance. And it must not be thought that special training in neurology necessarily enables the observer to solve the problem—meningitis or toxæmia. Such special training, excellent asset though it is, sometimes leads to a false sense of security, in that its possessor is prone to attach too much importance to fine points in the symptom-complex of a particular case. If no more direct investigation of the state of the cerebral membranes were possible than a close scrutiny of the functions of the underlying brain tissue, itself sharing the inflammation, a condition of doubt must now and then be the inevitable result of the examination. From this state of ambiguity the physician is able, again and again, to arrive at a certain diagnosis by means of lumbar puncture.

The puncture should be employed, both in cases of suspected primary disease of the meninges, and also when meningitis is possibly complicating other morbid conditions of the central nervous system, such as cerebral abscess.

Not only is the question of the existence of meningitis often settled, but the equally important question of the cause of the meningitis (when present) is also often revealed. And thus both prognosis and treatment may be very definitely assisted. The value of the puncture in determining the nature of a meningitis will be discussed later.

(ii) *Chronic meningitis.* The above remarks have referred to acute meningitis (lepto-meningitis), a disease which would be better named 'acute meningo-encephalitis'. The indication for lumbar puncture is no less clear in suspected cases of *pachy-meningitis*, which is usually a chronic disease, of tuberculous, syphilitic, or traumatic origin, mostly spinal in its distribution, and often local.

(iii) When the toxæmic state referred to in the first section

is very marked, as it occasionally is in children suffering from pneumonia, and when at the same time there are no convincing signs of organic disease of the brain or meninges, the condition is sometimes termed *meningism* ('pseudo-meningitis'). This is undoubtedly one variety of what the older physicians understood by their word 'phrenitis'. And the popular expression 'brain fever' certainly covers many cases of this sort, thus accounting for the much higher percentage of recoveries from this condition than we know to occur from meningitis. Some eminent neurologists decline to mark off such cases from meningitis proper, or rather, conceive of them as being in reality mild instances of meningitis. And there is much to say for this standpoint on clinical grounds. But the course of the disease, the prognosis, and, above all, the characters of the cerebro-spinal fluid, completely justify the position of those who regard such cases as meriting a special category.

(iv) Any case of *coma* of doubtful nature is an indication for puncture of the spinal theca. The information to be derived from the proceeding can scarcely be overestimated. Contra-indication does not exist, for the insensibility of the patient removes even the objection of distress caused by the use of the needle. A fractured skull, previously unsuspected, may be suggested by the appearance of blood in the fluid. Uræmia may be clearly manifested by finding quite a high percentage of urea to be present (*vide infra*).

(v) It has been of late years clearly shown that *parasyphilitic affections* of the brain and cord lead to recognizable changes in the cerebro-spinal fluid. Both general paralysis of the insane and tabes dorsalis may thus be marked off in some degree from conditions simulating them, and the puncture is indicated in all doubtful cases of these two diseases.

(vi) In the diagnosis of *uræmia* lumbar puncture is of considerable service. Emery, as the result of several special observations, regards the chemical examination of the cerebro-spinal fluid as affording the simplest test of the functional capacity of the kidney. In one case he found urea present in as large a quantity as 0·4 per cent, or ten times the amount present in health. The present writer has found it as high as 0·1 per cent. According to Emery the content of the fluid in chlorides also rises, and the freezing-point is depressed, in this condition.

2. *Therapeutic indications.*

(i) *In the treatment of meningitis.* Periodic drainage of the spinal meninges, acting, it is thought, by removal of bacteria and their toxins, has been found of distinct benefit in some cases of acute meningitis. In the writer's own experience he has been quite convinced of this, as in the treatment of cerebro-spinal meningitis due to the meningococcus. In tuberculous meningitis the writer has seen, at most, temporary benefit derived from the puncture; others, however, speak of actual recovery resulting from the drainage; but it is difficult to believe that in such cases a true meningitis was present, seeing that this inevitably means generalized tuberculosis. In two cases of meningococcus meningitis in which a diagnostic lumbar puncture had been undertaken, the writer saw improvement leading to recovery commence from the time of the puncture. In three other cases the writer allowed a small canula to remain *in situ* for twelve, twenty-four, and forty-eight hours respectively, during which periods a large quantity of turbid fluid drained from the meninges, and there seemed little doubt that the operation was of assistance in recovery.

The occurrence of resolution in cerebro-spinal meningitis after lumbar puncture complicates the therapeutic argument in connexion with the use of specific sera and vaccines. Results are sometimes put down to the credit of these substances which it is not unreasonable to suppose were due to the withdrawal of some of the inflammatory exudate from the spinal canal. It is clear that the persistence of acute meningitis indicates removal of the effusion by lumbar puncture, and although there is a great difference between the benefit usually derived from such a proceeding and that seen to follow removal of a pleuritic effusion, there is undoubtedly an analogy between the two conditions which makes the procedure quite rational in the disease now under consideration. Moreover, this mode of treatment calls for no special pathological training on the part of the practitioner, seeing that it is merely the removal of the fluid, not its histological or bacteriological examination, with which the therapeutist is concerned.

(ii) *The relief of intracerebral pressure.* Short of influencing directly the course of a cerebral disease, whether meningeal or not, lumbar puncture may be performed to relieve tension. Coma is not infrequently replaced by temporary consciousness after the puncture, and it is likely that the progress of an optic neuritis may be delayed by this means, so that, in the event of ultimate recovery from the causal disease, there is less risk of sight being permanently lost. The puncture may therefore well be performed periodically in cases of rapidly developing optic neuritis in cases of cerebral tumour due to syphilis, pending the action of anti-syphilitic drugs. This treatment has obvious advantages over trephining, which has been performed with the same object in view, but which may well be reserved as a more permanent measure if necessity arise.

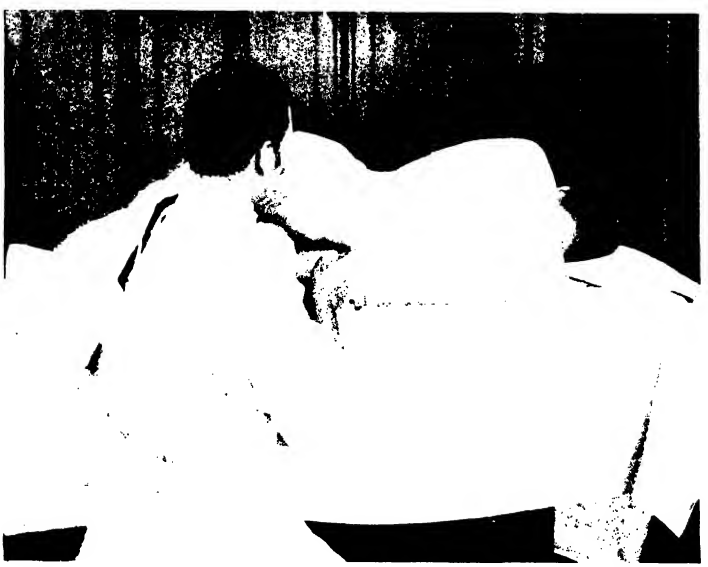
(iii) *The relief of headache.* Temporary, but sometimes very marked relief from headache may follow the puncture. The writer has seen this occur in cerebro-spinal meningitis, in cerebral tumour, and in uræmia. Emery refers to a similar beneficial effect in chlorosis, but of this the writer has had no experience; the fact tends to supplement the evidence already forthcoming that there is a definite toxic element present in this disease.

### III. TECHNIQUE

1. *Position of the patient.* In the majority of cases the patient is acutely ill, and the recumbent posture is for this reason obligatory. He is placed on his side near the edge of the bed, with knees drawn well up, head bent forwards, and trunk arched with convexity backwards, so that the laminæ of the vertebral column are opened as far as possible. Care is taken that the lower shoulder is not resting upon a pillow or upon a raised part of the bed, otherwise the line of the spine is not straight, as is desirable. If the patient is not acutely ill, he sits on the side of the bed with arms folded and body bent forwards.

2. *Surface-marking for the puncture.* The dorsal spine lying nearest to the transverse line which joins the summit of the crests of the iliac bones is that of the fourth lumbar vertebra. The puncture is best made between the third and fourth lumbar vertebræ. The spines of these two bodies are therefore marked with an aniline pencil, and a point is chosen, in the case of an adult, about a third of an inch on one side of the mesial line, at an equal distance from each spine. It is well to mark this point on each side of the mesial line. The reason for making the skin-puncture a little to one side of the mesial line is that the tense ligaments lying underneath it

# Plate III



Illustrating technique of Lumbar Puncture.

are thus avoided. In children and in infants the puncture is made in the mesial line.

3. *Preparation of the skin and apparatus.* The skin is prepared as for other punctures. Rubbing by swabs, using soap and water, followed by alcohol, or ether, or acetone, is the best treatment. While the skin is being prepared a 10 c.c. syringe, with a stout needle measuring at least three inches in length, is being boiled close at hand. A long needle having a metal block at its proximal end to serve as a handle, may be used instead of a syringe and needle. Or, if the patient be anæsthetized, a trocar and canula may be used.

4. *The question of anæsthesia.* A general anæsthetic is only advisable if the patient is delirious or is a child (not an infant) of such an age that it cannot appreciate the fact that very little pain will be caused by the procedure. In either of these conditions an anæsthetic should be used, to avoid movement of the body, and especially to avoid arching of the back with the convexity forwards as the prick of the needle is felt. Some degree of this arching (opisthotonus) may be incidental to the disease, especially in infants. In all other cases no anæsthetic is required, although some operators use an ethyl chloride spray to the skin. The objections to this are the discomfort caused by the process of freezing and the hardness of the skin when frozen. If no local anæsthetic be used, a little ether or alcohol is allowed to run over the seat of puncture immediately before this is made, thus completing the sterilization of the surface.

5. *Making the puncture.* The needle is inserted at the spot already indicated and is directed forwards, with a slight inclination upwards and inwards. In the case of an infant the direction is made wholly forwards. If obstruction

be encountered this is probably by bone; the needle is withdrawn a little way, and the direction is slightly altered until the canal is entered. Very gentle suction is now exercised by the piston. If no fluid enters the syringe suction is not to be continued. By far the commonest cause of a 'dry puncture' is the fact that the needle has not entered the spinal canal; less common causes are the striking of a nerve-root and the presence of an inflammatory exudate that is too inspissated to flow through the needle. If, from the 'feel' of the needle during the puncture, the operator considers it probable that the theca has been reached, it is well to detach the syringe and pass the (boiled) stylet through the needle. If there is still no flow when the stylet is removed, the needle is entirely withdrawn, is tested for patency, and the puncture is repeated on the opposite side of the mesial line. If these directions are followed the probability of a successful operation is very high indeed. A little practice, however, is naturally of much assistance. Such practice may be readily secured by a few days' attendance in the post-mortem room.

### IV. EXAMINATION OF THE FLUID

The advantage of using a syringe is that the fluid is collected in this and contaminations from the air are avoided. If no syringe be used the fluid is allowed to drip directly into culture tubes or into a sterile test-tube. In this latter case it is advisable to neglect the first few drops of the fluid. A complete cytological and bacteriological examination necessitates laboratory methods, and if this is required the fluid is transferred to a sterile vessel and this is forwarded immediately to the pathologist. Certain important facts can, however, be made out at the bedside, and these it is well to investigate forthwith. They are the following :—

1. The pressure under which the fluid flows.

2. The naked-eye features of the fluid, whether clear, turbid, purulent, or blood-stained.

3. The presence of albumin, of reducing substance, and of urea.

The further examination of the fluid includes—

4. The presence of cells and their nature.

5. The presence of micro-organisms and their nature.

In the full investigation a careful consideration is given to all these points, which may well be touched upon here without entering into the various practical steps with which the laboratory work is concerned.

1. *Pressure of the fluid.* To those unaccustomed to perform lumbar puncture the fluid, even in health, appears to flow, at first at all events, with more force than is expected. It is known that the fluid is secreted under a positive pressure. In disease this pressure is sometimes exceeded ; occasionally it is very high, so that the piston is pushed up the barrel of the syringe and no suction is needed to fill it. If a simple trocar and canula be used, the fluid may spurt some distance on removal of the trocar ; in one case of cerebral abscess in which the puncture was made by the writer the fluid was shot out to a point several feet away.

2. *Naked-eye appearance of the fluid.* In health the cerebro-spinal fluid is clear, limpid, and colourless, forming no deposit on standing. In disease it may vary from this condition, through different degrees of opalinity, up to one of such turbidity as to suggest thin pus. Thick pus is scarcely ever seen. Flakes of unorganized protein matter are very common in cases of meningitis, even when the fluid as a whole shows little or no turbidity. Blood may be present, either because (*a*) a vessel has been wounded during the puncture, or (*b*) the effusion is blood-stained, or (*c*) blood

has entered the cerebro-spinal system at some point as the result of trauma (e.g. fractured skull). In (*a*) the added blood usually colours the first portions of fluid only and the colour is at most a very pale red, more often a straw colour; in this case it is desirable to preserve the blood-stained portion separately. It serves well for culture purposes, as the blood favours growth of most pathogenic micro-organisms, the meningococcus especially. But the presence of blood disturbs the cytological investigation, so that for this purpose the later portions of the fluids are used. In (*b*) the fluid is bloody throughout and definitely red: hæmorrhagic meningitic effusion is rare. In (*c*) the amount of blood is apt to be considerable; it is, of course, present during the whole time of the flow.

3. *Chemistry of the fluid.* In health cerebro-spinal fluid has a specific gravity of 1003–8, is faintly alkaline in reaction, contains a minute trace of albumin, and reduces Fehling's solution. Changes in the specific gravity are slight in disease, and are probably of no diagnostic significance. If albumin be present in sufficient amount to give a definite cloud with the heat and acetic acid test, or a ring with cold nitric acid, a certain indication of disease is given. Sometimes albumin may be present to a degree that can be estimated by Esbach's method. The reducing action of the fluid is said by some observers to be absent in meningitis (see p. 102). A trace of urea is present in health, but probably too small an amount to react to ordinary tests. It is increased in uræmia.

4. *Cytology of the fluid.* A film prepared from the deposit which forms at the bottom of the tube, and stained by Jenner's fluid, may show the presence of cells, the characters of which will be revealed. In health an occasional lymphocyte may be present—one or two at most in a field under a sixth objective. The actual number, as

estimated by the Thoma-Zeiss pipette, is usually less than 10 per cubic millimetre of the fluid. In disease the number of lymphocytes may be much increased, or polymorphonuclear cells may be also, and mainly, present.

5. *Bacteriology of the fluid.* In the same film search is made under a twelfth objective for micro-organisms, intra- and extra-cellular in distribution. The bacteriological part of the examination especially needs the support of laboratory methods for its completion. But the morphology and the intracellular distribution of the meningococcus are such characteristic features of this micro-organism that to find a small intracellular diplococcus present constitutes at once an almost certain diagnosis of cerebro-spinal meningitis.

## V. INTERPRETATION OF RESULTS

The routine examination of lumbar puncture fluid in diseases of the central nervous system, and in some other conditions, has not yet been undertaken sufficiently long to justify more than certain broad conclusions. These conclusions can be most conveniently considered under the heads of the different disease processes in which the cerebro-spinal fluid is apt to be altered in its composition. The alterations will be discussed in the order already adopted (physical, chemical, histological, and bacteriological), the various laboratory findings being also added.

1. *Acute Meningitis.*

The fluid usually loses its clear and limpid look, and becomes faintly opaline or definitely turbid. Albumin is increased, and the reducing action is often lost. There is considerable difference in the statements made with regard to this latter point. French observers lay stress upon the 'absence of sugar' in the fluid in cases of meningitis, and it is probable that by absence of sugar they mean

absence of reducing power. It would appear that the reducing power of the normal fluid is due to pyrocatechin (Halliburton), and although some observers hold that a small quantity of dextrose is also present, this is not sufficient to reduce Fehling's solution any more than is the small amount of sugar present in normal urine. The writer is quite unable to confirm the above observation of French physicians, and Dr. Ernest Shaw found that in 30 cases of meningitis in which he paid special attention to this point, reduction was present in no less than 24 cases (80 per cent). In the second edition of Emery's book the statement of the French school is upheld, but in the third edition the author, though still attaching great importance to the test, admits that he has met with several cases of tuberculous meningitis in which reduction was obtained in slight degree. So far as the chemistry of the fluid goes it may be said that *an increase of albumin gives strong presumptive evidence of meningitis, and if in addition the reduction of Fehling's solution does not occur, the diagnosis of meningitis may be said to be almost certain.*

The cell content of the fluid, and its bacteriology, differ according to the nature of the infecting agent; so also, in degree, does the chemical composition of the fluid.

(i) *Tuberculous meningitis.* As already mentioned, the turbidity may be very slight, or the fluid may even appear natural to the naked eye. Occasionally the fluid is clear but contains a few whitish flakes. The amount of albumin is often quite small, and may not be sufficient to estimate by Esbach's tube. The centrifugalized deposit contains a number of leucocytes, and, following the rule fully referred to in the chapter dealing with pleuritic effusions, the majority of these are usually lymphocytes. Occasionally, however, the rule is departed

from. One of the figures illustrating a recent article by Dr. Graham Forbes dealing with the pathology of cerebro-spinal fluid, shows an excess of polymorphous cells to the extent of over 70 per cent in a case of tuberculous meningitis. The *tubercle bacillus* is more constantly found in lumbar puncture fluid than in pleuritic effusion, but the search is rarely an easy one. Perhaps the best method is to allow the fluid to sediment without centrifugalization. In the small deposit that usually forms is found a minute clot, and in the meshes of this clot the tubercle bacilli are entangled. The clot is therefore dealt with as in the examination of sputum for tubercle bacilli. Adopting this simple method, Forbes was able to demonstrate bacilli in no less than twenty-five out of thirty-one (i.e. 80 per cent) cases of tuberculous meningitis. The absence of micro-organisms in films and on ordinary culture media are themselves facts that favour the presence of tuberculous meningitis in any case where the clinical condition suggests this diagnosis. The same devices are employed to discover the bacillus in cerebro-spinal fluid as in pleural fluid. But it is obvious that animal inoculation, which takes four weeks at least to give a positive result, is of no assistance in the diagnosis of a disease which is usually fatal within the same period of time.

*Summary.* Tuberculous meningitis is probably present if, in any case where the symptoms are suggestive of meningitis, the cerebro-spinal fluid contains an increase of albumin, and if its cytology shows a lymphocytosis. Tuberculous meningitis is proved to be present by the discovery of the tubercle bacillus in fluid having these characters.

(ii) *Meningococcus meningitis* (cerebro-spinal meningitis; cerebro-spinal fever; post-basic meningitis; cervical opisthotonus of infants). The turbidity of the puncture fluid

is usually well marked, except in late stages of an acute case, or in a chronic case ; white flakes are also usually present. Albumin is more marked than in tuberculous meningitis, and can often be estimated quantitatively by Esbach's method. Reducing fluid may be absent. The deposit contains as a rule a large number of cells, and the dominant cell is the polymorphous leucocyte. But with regard to the question of cytodiagnosis the same comment holds good here as with pleuritic exudates : in the late stages of the disease, and occasionally throughout if the case be not acute, the lymphocyte may be in excess of the polymorphous cell. The writer has seen 80 per cent of lymphocytes present in a case of well-marked cerebro-spinal meningitis in a young adult, the fluid showing meningococci in the films and on culture. The films may show a scanty distribution of small round diplococci, generally lying in the cells. In many cases prolonged search has to be made before a pair of cocci is seen. But the appearance is so characteristic that, when found, the nature of the meningitis is almost certain. The only other condition leading to a somewhat similar appearance is gonococcal meningitis ; but this is a rare disease, whereas meningococcus meningitis is common. Both micro-organisms are Gram-negative, and their ultimate differentiation turns upon cultural features. In not a few cases no meningococci can be seen in the films, yet cultures are positive without difficulty. In some of the cases of post-basic meningitis the cultures are repeatedly sterile ; it is then probable that the infective stage of the disease has passed.

*Summary.* Meningococcus meningitis is probably present if, in a case where the symptoms are suggestive of cerebro-spinal fever, the cerebro-spinal fluid is turbid, if it contains a large amount of albumin, and if its cytology shows a

preponderance of polymorphous cells. Meningococcus meningitis is almost certainly present if, in addition, films show intracellular, Gram-negative diplococci; it is proved to be present if the meningococcus is isolated by culture.

(iii) *Pneumococcus meningitis.* The purulent character of the fluid is apt to be even more marked than in (ii). The albumin is present in considerable amount. The polymorphous cells are in great excess, and the pneumococcus is usually readily demonstrated, both in the films (where it is chiefly extra-cellular) and on culture.

(iv) *Streptococcus meningitis.* This is the form most often seen to complicate middle-ear disease. The general features are the same as in (iii), but one or other type of streptococcus is present. Most often the type is *S. pyogenes.* But cases of meningitis due to the type *S. fœcalis* have been observed.

(v) *Staphylococcus meningitis* is not common. A staphylococcus infection may be secondary to ear disease or it may complicate meningococcus meningitis : the writer has seen three instances of this mixed infection. The general features are again those of (iii).

(vi) *Influenzal meningitis* is a condition often talked about, and it certainly occurs. But, strangely enough, few cases are authenticated by means of lumbar puncture. The writer recently saw a case with Dr. Pearce, of Bushey. In a patient under Dr. Ormerod's care at St. Bartholomew's Hospital from whom the writer once failed to get fluid by puncture, it was found at the post-mortem that the exudate consisted of thick curdy pus, which yielded a growth of *B. influenzæ* and *pneumococci* in about equal quantities.

(vii) The *gonococcus, B. typhosus, B. anthracis* and *actinomyces* have all been found in lumbar puncture fluid in a few instances.

2. *Meningism.*

Reference has already been made to the occurrence of meningeal symptoms in children during the course of pneumonia and some other acute diseases, the cerebro-spinal fluid giving no definite evidence of meningitis. At present very few lumbar puncture observations have been made in such cases. Such few as are available tend to show that the albumin of the fluid is slightly increased and that there is a slight increase in the lymphocytes normally present. The reduction of Fehling's solution occurs as in health. The condition evidently indicates a state of meningeal irritation which is morbid, yet has not the characters of acute inflammation. Such cases usually run a favourable course, and the value of lumbar puncture from the point of view of prognosis is in this connexion very high.

3. *Chronic meningitis.*

(i) *Syphilis* not infrequently produces a spinal pachy-meningitis. The fluid is clear or slightly turbid. The albumin content is high; in one case the writer found it to measure between 0·1 and 0·2 per cent by Esbach's method. The protein in these cases is said to be chiefly globulin. Cells are not present in very large numbers, but they are considerably more numerous than in health; they are almost wholly lymphocytes. Cultures are sterile. The recognition of the disease is of fundamental importance, as intensive mercurial treatment may lead to complete cure without any permanent damage being done to the nerve structures.

(ii) *Tuberculosis*, in the form of Pott's disease, not infrequently leads to a state of things almost exactly similar to (i) and indistinguishable from it so far as the chemistry and cytology of the fluid go; but a careful search may

demonstrate the presence of the tubercle bacillus. Wassermann's test also serves to distinguish the two conditions.

(iii) Some cases of *meningococcus* meningitis are chronic, especially the so-called post-basic meningitis of infants (cervical opisthotonus of Gee and Barlow). The *meningococcus* may or may not be obtained by culture; but, as already mentioned, the cytology is apt to vary from the customary rule, and show an excess of lymphocytes rather than of polymorphous cells.

4. *Parasyphilitic diseases* of the brain and cord.

In *tabes dorsalis* and in *general paralysis of the insane* the changes in the cerebro-spinal fluid are now known to be highly suggestive. The protein present is generally increased, though not to any large amount. It is of the nature of globulin, and yields a thin white ring when a little of the fluid is poured gently on to the surface of a saturated solution of ammonium sulphate in a test-tube. This constitutes the 'ammonium sulphate test'. It has also been shown that the addition of a weak solution of butyric acid, heating, and subsequent addition of a little sodium hydrate, leads to the presence of a flocculent precipitate (Noguchi's test). Cytologically considered, there is usually a definite lymphocytosis present in both of these parasyphilitic affections. It must not be forgotten, also, that the removal of some cerebro-spinal fluid permits of the application of Wassermann's test. If this test prove to be positive it is probable that the condition is syphilitic rather than parasyphilitic; a positive test is therefore a definite indication for active medication on antisyphilitic lines. In parasyphilitic affections (as tabes and G.P.I.) it is more common to find that, though the patient's blood yields a positive reaction, the cerebro-spinal fluid does not.

# CHAPTER IX

## INFECTIVE CONDITIONS OF THE NOSE, MOUTH, AND THROAT

UNLIKE the blood and the cerebro-spinal fluid, which are in health free from micro-organisms, the mucous membranes lining the air passages and the alimentary canal are the nidus of innumerable bacteria. These bacteria are usually spoken of as 'non-pathogenic', but it should be noted that there is no hard-and-fast line to be drawn between non-pathogenic and pathogenic micro-organisms when the mucous surfaces of the body are concerned. It is generally conceded, for example, that the pneumococcus which is found in normal saliva, though a harmless inhabitant of the mouth and throat during health, may become highly injurious, causing serious diseases. This change is supposed to be due, either to a more or less sudden attainment of virulence by the germ or to a lowering of the vitality of the patient, or to both of these events. What is true of the pneumococcus is true also of the streptococcus. There is a strain of streptococcus constantly present in the normal mouth (*S. salivarius*) and causing no disturbance in health. In the condition known as pyorrhœa alveolaris, however, this streptococcus is found to be definitely pathogenic, producing a series of morbid changes around the teeth with consequent disease. There is no doubt that microbic activity at the orifices of the body, and especially at the orifices now under consideration, is responsible for very many conditions of ill health which go unexplained. The subject is a large one.

In this chapter some practical hints will be given concerning the investigation of various materials available for examination, and reference will be made to possible results.

## I. THE NOSE

It is often advisable to make a bacteriological examination of a nasal discharge. A little of the discharge should be smeared on a couple of slides, as in the examination of pus. If culture tubes are available these should also be inoculated. If, however, it is desired to send the discharge as such to the pathologist, the writer finds that a clean and folded handkerchief serves the purpose very well indeed. The inside of such a handkerchief is usually sterile, probably owing to the fact that it is treated with a hot iron whilst being folded. The patient opens the handkerchief, blows the nose into its centre, folds it up carefully but loosely, and forwards it to the pathologist in an air-tight tin box.

1. In *acute coryza* or acute rhinitis with pharyngitis (' common cold ') cultures of the nasal discharge rarely yield a single micro-organism. Occasionally, however, the result is an almost pure culture of *M. catarrhalis*, of *pneumococcus*, or of *B. coryzæ segmentosus*. More often the growth is a mixture of one or more of these bacteria with *streptococci*, *staphylococci*, *B. influenzæ*, Friedlander's bacillus and various diphtheroids.

2. The occurrence of *nasal diphtheria* is such a common event, and is so often overlooked, that this alone justifies an examination of all chronic nasal discharges that are purulent. Pieces of membrane are occasionally seen in the discharge, and these are specially useful for examination by films and cultures. The pathologist will report whether any diphtheroid bacillus obtained in a doubtful case is to be regarded as a true diphtheria bacillus (Klebs-Loeffler) or the pseudo-diphtheria bacillus (Hoffmann); the occurrence of the former

micro-organism is to be regarded as conclusive proof of true diphtheria, whereas the presence of the latter is a point of no practical significance at all.

3. *Chronic rhinitis*, whether purulent or non-purulent, is associated with the micro-organisms enumerated under 1. Their isolation is important, because much can sometimes be done to check or to cure the trouble by appropriate vaccine treatment.

4. The discharge may be a result of *antrum* or *frontal sinus* disease—a state of things that must be determined by clinical examination.

## II. THE MOUTH

1. Bacteriological examination of the *saliva* is of little or no value in disease because this fluid contains so many and such a variety of microbes during health—never less than 10,000,000 per cubic centimetre (M. H. Gordon).

2. *Ulcers* and *aphthous patches* should be cleaned by sterile cotton-wool, and then scraped firmly with a stout platinum wire, transferring the material thus obtained to slides and culture tubes. In *ulcerative stomatitis* this investigation may be of much service.

3. The most important infective process met with in the mouth is *pyorrhœa alveolaris* (Rigg's disease). The great clinical importance of this disease can only be incidentally referred to here. It is quite true that a severe grade of the affection may exist without much or indeed without any constitutional disturbance. But on the other hand, it is also true that this condition of the teeth and gums may be responsible for far-reaching effects upon the general health, some of which, if this possible cause be not borne in mind, present great difficulty in their elucidation. Absorption of toxic substances formed in this infective process may lead to direct effects

upon the digestive organs, or may indirectly lead to anæmia, arthritis, malnutrition, and various nervous phenomena. One of the most interesting observations in connexion with pyorrhœa alveolaris is the simulation of hæmoptysis, or of hæmatemesis, which occasionally occurs in patients who are the subjects of the disease. The writer once saw, in the same day, two patients who were thought to be phthisical on account of supposed hæmoptysis, loss of weight, and dyspepsia, in both of whom the source of the bleeding was pyorrhœa alveolaris. One of these patients had been sent to a sanatorium for treatment. The appearance of the blood, which is often produced in the early morning in these cases, is characteristic : it is free from air and sputum, and is watery in consistency.

In taking the pus for investigation from a case of pyorrhœa alveolaris it is almost useless to collect the material that lies ready to hand on the surface of the gums. This usually consists of a mixture of tartar, food particles, and pus, and when it is remembered that the pockets in the gums between the teeth are small sinuses which are crowded not only with the primary infecting agent, but with all manner of secondary invaders from the saliva, it will be seen how next to impossible it may be for the bacteriologist to isolate with any certainty from his cultures of such flora the actual cause of the malady. To obtain a specimen of the pus which will be of service it is necessary to dry thoroughly the surface of the gum just above the pocket which is being examined, using sterile absorbent wool. The gum is then massaged, and the pus which exudes is also wiped away carefully. Massage is now again employed, squeezing the pus well from the bottom of the pocket. This material is now taken up with a platinum loop and tubes of sloped agar-agar are directly inoculated with it. Plate IV shows the difference in actual growth

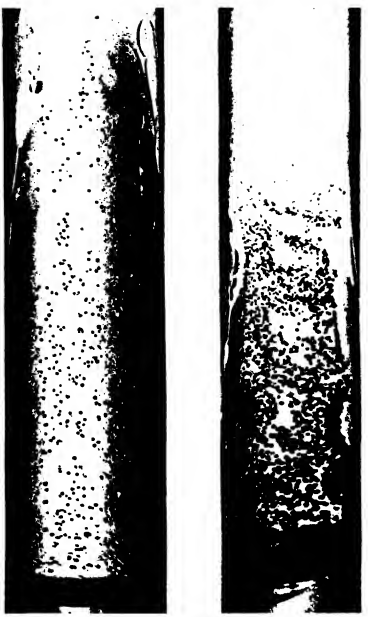
between a culture taken from the pus lying about the gums, and a culture taken after exercising the above precautions. In the second tube a very mixed growth is obtained, from which it is difficult to obtain any micro-organism in such dominant numbers as to convince the bacteriologist that he is dealing with the causal infecting agent. In the first tube the great majority of the colonies are streptococcal, and this fact indicates the real nature of the infection. Sometimes a still better method of obtaining the certain microbic cause of the infection is possible, that is, when a tooth which is affected by the disease process is extracted. Cultures made from the fang of such a tooth, as the dentist holds it in his forceps, give the best results of all. On three or four occasions the writer has obtained pure cultures of a streptococcus by this method, and, when this has been the case, it has been possible to make up a series of doses of vaccine at once from this original culture.

When care is taken to avoid dealing with the causes of secondary infections, and when the pus is obtained from a place as near to the peri-odontal membrane as possible, it is found that the micro-organism obtained is the type of streptococcus termed by Andrewes and the writer *S. salivarius*. The writer believes pyorrhœa alveolaris to be a specific disease, and always to be due to streptococcal infection.

### III. THE THROAT

In the great majority of cases in which it is desirable to obtain material from the throat for bacteriological examination, the seat of inflammation is one or both tonsils. It should be remembered that if there is a definite patch of exudation to be seen, it is very desirable that this patch, and not the whole arch of the fauces or even the whole surface of the tonsil, should be made the object of investigation. A

# Plate IV



Two culture-tubes of sloped agar-agar inoculated with pus from a case of pyorrhœa alveolaris. In the first tube the material for inoculation has been taken from the fang of an extracted tooth. In the second tube the material has been taken from a pocket in the diseased gum. The first tube shows an almost pure culture of streptococci. The second tube shows a mixed growth, chiefly of staphylococci.

platinum loop directed on to the surface of such a patch will bring away material which is more valuable than may be obtained by a swab which, perchance, becomes contaminated by saliva during its insertion or removal. In all such examinations it is imperative to use a good light, and to have the patient in the best possible position for the purpose of the examination; in other words, it is imperative that the operator should see exactly what he is doing. If there is any membrane present on the fauces, a bit of this should be removed by a pair of fine-nosed forceps and forwarded for examination in a small glass tube fitted accurately with a rubber stopper or ordinary cork. Such material is invaluable for the investigation. Swabs that are used for throat cultures should be sent away in air-tight tubes, so as to avoid desiccation of the material conveyed upon them. If a little of the exudate be spread out into a thin film on a glass slide, dried slowly, and forwarded to the pathologist with the swab, the investigation is made more valuable. Or this film may be at once examined by the practitioner. It happens not seldom that by the examination of such a film the observer can say positively that the diphtheria bacillus is present, and this without waiting for the cultures to be incubated. This expedition is possible when certain differential staining methods reveal the presence of numbers of bacilli in the film having the morphological characters of the Klebs-Loeffler bacillus (Neisser).

It may not be out of place to refer here to the value attaching to the bacteriological diagnosis of *diphtheria* in general. It must constantly be borne in mind that *whereas a positive report concerning a throat swab makes the diagnosis certain, a negative report carries only presumptive evidence against diphtheria being the cause of the sore throat.* If, therefore, the clinical condition of the patient is strongly suggestive of the disease in question, appropriate treatment must be

adopted forthwith, and must be continued in the face of a negative report. This being so, it may by some be said that the bacteriological investigation is of no service. On the contrary, it is of the utmost value. (1) It proves some cases to be diphtheria which are, from a clinical point of view, quite equivocal. (2) It often enables the practitioner to decide whether the initial dose of antitoxin given as a safeguard in a doubtful case shall be repeated. (3) It sometimes assists very materially in tracing the source of infection, both in a single case and (of great importance) in epidemics, to a ' carrier ', such as a person having a chronic nasal discharge. (4) It is the most certain means of deciding when a patient ceases to be infectious.

In *tonsillitis*, *quinsy*, and other forms of sore-throat, the procedure is the same as in suspected diphtheria.

In cases of suspected *syphilis*, during the secondary stage, it is advisable to examine the secretion on the tonsils by the direct method of dark illumination. Spirochætes may not seldom be demonstrated in this way, even in cases where there are no condylomata.

### IV. THE POST-NASAL SPACE

Material from the vault of the pharynx may be obtained for bacteriological examination by a device introduced by Mr. C. E. West. A metal speculum, curved almost to a right angle at an inch from one end, has the edges of the opening of the short limb slightly everted. This tube carries a twisted copper wire, armed with a small plug of sterile cotton-wool which can be withdrawn into the tube or projected beyond the end at will. By this instrument any mucus or other material that has previously been seen in the post-nasal space may be removed without contamination by micro-organisms from the mouth, and may be submitted to cultivation.

# CHAPTER X

## INFECTIVE CONDITIONS OF THE URINARY TRACT

THE materials requiring investigation in connexion with the diagnosis of these infections are two—*pus* and *urine*. Semen may occasionally be available for this purpose, but it may be dealt with on lines similar to those adopted in regard to pus. Speaking strictly, a 'gleet' offers still another kind of material, but here again the methods are those used for pus, and between the thin mucous secretion of a long-standing gleet and the thick pus of an acute gonorrhœa all transitions are to be met with. Considerable variations in the consistency of a urethral discharge are not seldom found in the same patient at different times; in which case it is advisable to deal with more than one specimen if a negative or equivocal result is obtained at first.

1. *Pus.* All material that is discharged from the urethra, either spontaneously or after pressure, should be dealt with in two ways: films should be prepared directly, and tubes of suitable media should be inoculated at once, or after arrival at the laboratory if tubes be not available when the pus is obtained. In the latter event the pus should be drawn up into a wide capillary tube, previously sterilized, the ends sealed in the flame, and the tube should be carefully packed and sent to the pathologist. The pus is drawn into the tube by capillary action if the material is sufficiently thin; if too thick for this method the necessary suction is provided by attaching a rubber bulb to the large end of the tube.

The films are of great value in the diagnosis of *gonorrhœa*,

as the intracellular disposition of the *gonococcus* is one of its most distinctive features. The cytology of the material also gives some guide to the nature of the inflammation : in gonorrhœa the pus often shows an unusually large number of eosinophil cells.

In a large number of cases of gonorrhœa the causal micro-organism is present in such small numbers, and grows with such difficulty, that it is necessary to inoculate a blood-agar plate with the material obtainable forthwith, if a culture is desired. This means that it is sometimes necessary for the patient to be seen by the bacteriologist for the purpose. The culture not only enables the pathologist to confirm a diagnosis of gonorrhœa suggested by the films ; it yields a growth of *gonococci* that may be used for purposes of preparing a vaccine. The culture also shows the presence or absence of secondary infection (by *staphylococci*, *B. coli*, &c.). Or it demonstrates the pus to be due to a primary infection by one of these last-named micro-organisms, or by some other infecting agent.

The pus from a urethra occasionally yields no growth of bacteria—as when it results from the application of caustics (silver nitrate, &c.) to the mucous membrane at some portion of the tract.

2. *The urine.* In the case of female patients, all specimens of urine that are to be submitted to bacteriological examination should be obtained by the use of a sterile catheter. The first few drops of the urine are neglected, the rest is collected in a sterile bottle with glass top, or (if the laboratory be handy) sterile cotton-wool. As a second best, an ordinary medicine bottle and new cork, both recently boiled, will serve. In male patients, though the use of a catheter is again an advantage, it cannot be said to be necessary, if the urine can be dealt with in a few hours

after its collection. It then suffices to clean the glans with soap and water, dry it with sterile wool, and allow the patient to pass water directly into the sterilized bottle, again neglecting the first few drops.

In dealing with the urine the bacteriologist will make cultures from the specimen as a whole, using known quantities of the material, and will also cultivate the deposit obtained after allowing the urine to stand or after centrifugalization. From the sediment, films will be made and stained. If the search be made for the *gonococcus*, any 'threads' present will be carefully scrutinized in film preparations. If little or no sediment be obtained on centrifugalization, the surgeon may deem it desirable to massage the prostate after the patient has retained his urine for some hours. On then passing his urine, the patient may discharge a fair amount of muco-pus, which is of great value for examination.

The commonest micro-organism present in infections of the bladder or pelvis of the kidneys (*cystitis ; pyelitis ; pyelocystitis*) is the *colon bacillus*. It is very easily seen in films, and is very easily grown on artificial media. In the absence of pus from the urine, the mere presence of a few *B. coli* does not necessarily denote disease : this state of things is exceedingly common, both in adults and in children, and especially in females. Both constipation and diarrhœa appear to favour the appearance of the bacilli, and they occur in the urine of a large proportion of all febrile patients. In the condition termed 'bacilluria' it is usually the *colon bacillus* that is present—the urine may, in these cases, appear quite turbid with bacilli, and yet the amount of pus be quite insignificant. *B. typhosus* occurs frequently in the urine of typhoid patients, especially during the third week of the disease. A bacilluria may be present in this

disease. *B. proteus* is a not uncommon infecting agent in the bladder. *Staphylococci* and *streptococci* also occur. Mixed infections are fairly common.

The *tubercle bacillus* requires special mention. It may occur alone or (not infrequently) as a mixed infection with *staphylococcus albus*; indeed, the isolation of *staphylococcus albus* from a purulent urine should always suggest the possibility of a tuberculous infection. Tuberculosis of some part of the urinary tract, or of the kidney substance, is such a common condition, that the urine must always be searched carefully for this microbe in any case of doubtful nature in which symptoms are referable to these structures. It must not be supposed that it is only in cases of pyuria that the tubercle bacillus is found in the urine. Tuberculosis of the kidney may show itself by hæmaturia, sometimes intermittent, without pus in the urine, and the tubercle bacillus may be isolated from such urine. In some cases the urine may appear quite natural to the naked eye, yet the microscope may reveal, in a small deposit obtained by centrifugalization, tubercle bacilli in appropriately stained films. It is rarely easy to demonstrate the bacillus in urine—in most cases where it is present the search has to be both careful and prolonged. In a few cases, however, the demonstration is not difficult, and it is well to assume first of all that the ordinary methods, which the practitioner is able to use himself, may be successful in showing the presence of the bacillus. Should they not do so the urine may be forwarded to the bacteriologist. He will scrutinize the centrifugalized deposit, and, failing to demonstrate the bacillus by films stained by the carbol-fuchsin and acid method, he will proceed to the inoculation of a guinea-pig in any case which is regarded by the clinician as possibly one of tuberculosis of the kidney or urinary tract.

# CHAPTER XI

## JOINT PUNCTURE

It is sometimes advisable to puncture a diseased joint in order to ascertain the nature of the fluid in it, and in order to investigate this fluid histologically and bacteriologically.

The *technique* of this procedure is very simple. The affected joint is placed in such a position as will remove the bones from apposition as far as possible. Thus, in the case of the knee-joint, which most often calls for this examination, the extended position is best, because the patella is thereby out of contact with the long bones. That part of the joint is selected for the puncture where the fluid is seen to be most apparent. If, in the knee-joint, there is a uniform swelling, the puncture is best made just beneath the patella, so as to avoid injury to the cartilages of the femur and tibia. A clean and sharp needle is chosen. The skin is thoroughly washed with soap and water, and afterwards treated with alcohol or ether. A local anæsthetic may be used, but is not of much service. Very little distress is caused to the patient if the needle is sharp and clean.

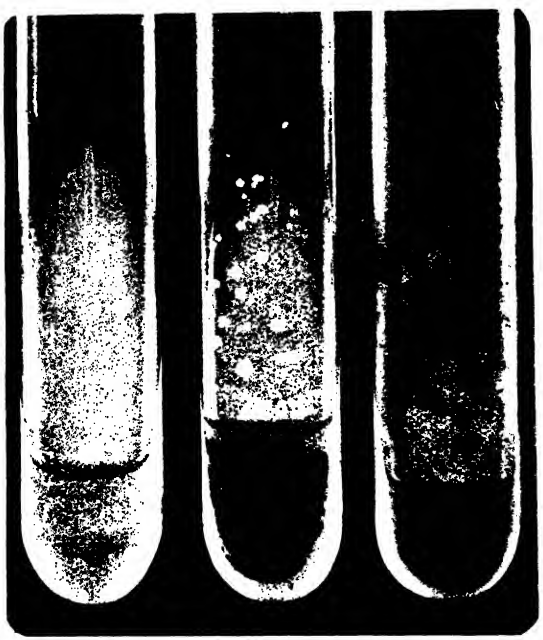
The fluid removed may be transferred to a sterile glass-stoppered bottle, and may be forwarded to the pathologist for examination. Better still, it may be in part transferred to tubes of culture media at once, in the manner fully described in the chapter dealing with blood-culture. In cases of suspected *gonococcus infection* it is well to perform blood-culture at the same time as joint puncture. Some of the joint-fluid may then be mixed with the blood, and some

may be incubated without blood. Plate V shows the result that may sometimes be obtained if this method be adopted. The method has the additional advantage of demonstrating if the blood-stream contains gonococci as well as the joints.

The micro-organisms obtained by joint puncture, other than the gonococcus, are chiefly *streptococci*, *pneumococci*, *staphylococci*, and the *tubercle* bacillus. Others are rare. Some observers describe a specific diplococcus as being present in the joints in *rheumatic fever*, and consider that this finding is almost constant. The majority, however, describe constantly negative results in the examination of the joint-fluid in this disease.

The character of the fluid varies from the clear viscid synovia of normal joints, through slightly or very turbid fluid up to thick pus.

# Plate V



Three culture-tubes of agar-agar used in the investigation of a case of gonorrhœal rheumatism. The first tube has been inoculated with fluid derived from puncture of the knee-joint; it shows a very slight growth of gonococci on the agar slope just above the fluid. The second tube has been inoculated, first with the patient's blood and then with the joint-fluid. It shows a good growth of gonococci. The third tube has been inoculated with the patient's blood only. It remains sterile.

*To face p.* 120.]

# CHAPTER XII

## THE EXAMINATION OF THE FÆCES

### I. HISTOLOGICAL

PATHOLOGICAL examination of the fæces yields very important diagnostic evidence in various diseases. Direct microscopic examination reveals the histological elements present, both animal and vegetable, and the state to which these have arrived by the processes of digestion—an investigation which has been raised to a high level of thoroughness by a certain school which claims to be able to select, as the result of such daily observations, the kind of diet which will exactly suit the patient. The knowledge that his food is chosen in this way ofttimes increases greatly the confidence of the patient in his medical adviser. It must be confessed, however, that apart from the hypochondriac, few patients have much to gain from the science of ' coprology '.

The presence of *pus* in the stools can often be made out by careful naked-eye examination, supplemented by the microscope. If it is due to the rupture of an abscess into the bowel, the pus is likely to be of sufficient amount to admit of no doubt ; if it is due to ulceration its demonstration is much more difficult, because the pus cells are not easily recognizable.

Fragments of *new growth* may occasionally be demonstrated by appropriate staining methods. *Hydatid hooklets*, portions of *actinomycotic* tissue, and *amœbæ* are also to be made out from time to time.

### II. CHEMICAL

Chemical examination of the fæces demonstrates the amount of fat present, and the occurrence of blood when this is not apparent to the naked eye—two observations which are of great value in the diagnosis of pancreatic disease and ulceration of the stomach or bowel respectively. Chemical examination also decides the amount of bile pigment and its derivatives, and, together with similar investigations carried out upon the urine, assists in the diagnosis of diseases of the liver and gall-bladder.

### III. BACTERIOLOGICAL

Just as a bacteriological examination of normal saliva shows the mouth and throat to be a constant nidus of bacteria, so a similar investigation of normal fæces shows the intestine to possess a very rich flora in the way of micro-organisms. The bacteria present in greatest numbers are coliform bacilli and streptococci. Of the first group the type most often isolated is termed *B. coli communis*; of the second group the type most often isolated has been termed *S. fæcalis*. In health both of these micro-organisms appear to act as saprophytes, but either may take on a pathogenic action, giving rise to acute or chronic infective processes. These infective processes may (i) involve the mucous surface of the bowel only, as in colitis; or (ii) they may involve the peritoneum immediately adjacent to the bowel, as in perityphlitis, or organs which communicate more or less freely with the gut, as in cholecystitis; or (iii) they may lead to a systemic blood infection, as in malignant endocarditis.

Very little is known concerning the *quantitative* bacterial content of the fæces in different diseases. The labour involved in such knowledge is, of course, great. But it may

be possible soon to adopt some more rapid method of arriving at this knowledge than is now undertaken. Not only would such a method be of great use in the study of disease; it would be of great service in testing various remedies which are vaunted as diminishing the number of germs in the colon. It may well be questioned whether the 'pictures' of the flora seen in stained films of fæces before and after the treatment of patients suffering from mucus colitis in certain continental cities do more than add to the mental effect which constitutes so large a part of the 'cure'. At present quantitative estimations involve much 'spade work'; yet without them nothing of importance can really be said on the matter.

As regards *qualitative* investigations of the flora of the fæces much more is known, and much more help can be given in diagnosis and treatment. For the purposes of the examination a little of a fresh stool is collected in a clean tin or wide-necked bottle, taking care that there is a well-fitting top to the vessel. This is forwarded at once to the pathologist. If the stool contains mucus, or sloughs, or blood-clot, or pus, these are specially chosen for the examination.

It is essential that the pathologist shall receive, with the specimen, some details concerning the case, and some guide as to what the clinician wants in the way of investigation. The bacteriologist will invariably commence by making films direct from the fæces, and staining these by Gram's method, to get some idea of the relative quantity of micro-organisms that do, and do not, stain by this method. He will also make plates from the diluted material, using special media (such as that introduced by Conradi and Drigalski) for the purpose of differentiating the common (non-pathogenic) colon bacilli from those bacilli which, though morphologically similar, are in reality highly pathogenic, as

*B. typhosus*, *B. paratyphosus*, and Gaertner's bacillus. These last-named bacilli give rise to blue colonies on the magenta-coloured medium, whereas *B. coli communis* gives rise to red colonies. The blue colonies can then be sub-cultivated and various bio-chemical tests can be applied to them.

In *typhoid fever* the isolation of the causal bacillus from the stools is no longer the important proceeding that it formerly was. It is much simpler to obtain the bacillus from the blood during the first week of the disease. In many cases the application of Widal's test and the estimation of the leucocyte count make the isolation of the bacillus unnecessary for purposes of diagnosis.

In *paratyphoid* fever the isolation of the pathogenic bacillus from the stools is more important, because the clinical features of the disease are apt to be ambiguous and the blood gives no agglutination reaction with *B. typhosus*.

In *food poisoning* an investigation of the fæces may yield colonies of Gaertner's bacillus, a very important finding from the point of view of public health.

In *dysentery* either the bacillus of Flexner or of Shiga, both of them pathogenic types of *B. coli*, may be isolated.

*B. pyocyaneus* not seldom appears to be the causal agent in cases of colitis, both in adults and in infants. It may be the only pathogenic micro-organism found in cases of *ulcerative colitis*.

The *tubercle bacillus* must be searched for in fæces by the same methods adopted for sputum, urine, &c. Quite recently it has been stated that this bacillus is found in the stools in the majority of cases of pulmonary phthisis, but this observation appears to be based only upon morphological characters and the principle of acid-staining—inconclusive evidence for such an important statement.

### IV. PARASITOLOGICAL

A very important investigation in connexion with fæces, and one which is not made sufficiently often, is the search for the *ova of parasitic worms*. This should never be omitted in any case of obscure anæmia, fever (especially in children), or intestinal dyspepsia. There may or may not be an increase of mucus in the stools when worms are present. Attention is not seldom called to this examination of the stools for ova by finding eosinophilia on blood examination.

# CHAPTER XIII

## THE DIAGNOSIS OF TUBERCULOSIS AND ITS SPECIFIC TREATMENT

### I. GENERAL

THERE is probably no difficulty with which the physician is more often faced than the diagnosis of a doubtful case of tuberculosis. There is certainly no infective process to prove the presence of which is of more paramount importance for the patient. The question of physical signs will not be dealt with here, but it may be well to emphasize the warning that, however conclusive physical signs may appear to be, they should never lead to more than a strong presumption in favour of infection by the tubercle bacillus. Be the pathological process situate in the lung, or lymph glands, or urinary tract, or elsewhere, an effort must always be made to put the diagnosis upon a more exact basis than that of physical signs; physical signs are the signs of conditions, not of diseases. Instances could be easily multiplied of mistakes which have resulted from the omission of this precaution, to which no exception should ever be made. One instance will suffice. A youth came under observation on account of copious hæmoptysis. When this had ceased examination revealed physical signs of bronchopneumonia in the upper lobe of the left lung, with recession and very defective expansion of the chest wall in this region. There were some enlarged glands on both sides of the neck. Fever was present, and was of a markedly 'hectic' type; cough and night-sweats were prominent symptoms;

the patient was anæmic and wasted. A diagnosis of tuberculosis was made. The fever and wasting continued and the physical signs in the lungs increased in extent; the heart showed evidence of dilatation, and the patient died. At the post-mortem examination the disease was proved to be lymphadenoma. The bronchial glands were much enlarged, pressing upon the root of the left lung and causing a bronchiectasis. The dilated tube was ulcerated, and no doubt this was the cause of the hæmoptysis. Had the sputum been examined for tubercle bacilli a negative result, repeatedly occurring, would have raised doubts as to the nature of the disease and would probably have led to a correct diagnosis.

### II. THE DEMONSTRATION OF THE TUBERCLE BACILLUS

The physical signs being such as to suggest tuberculosis—or, physical signs being altogether absent, the symptoms suggesting tuberculosis—the first consideration is whether or not any material can be obtained from which the tubercle bacillus may be isolated. In a case of suspected phthisis an effort must be made to secure a specimen of sputum; and the practitioner must not be easily put off by the patient's protest that there is none (see p. 53). If the case is one of disease of the kidney or urinary tract the urine must be collected and subjected to special scrutiny. If the trouble is in the bowel or peritoneum the fæces must be examined. If any puncture-fluid be obtainable—as from the pleura, the spinal theca, or a joint—this is, of course, invaluable for investigation. By a variety of methods, varying with the nature of the material to be dealt with, the pathologist will endeavour to isolate the bacillus. (Some of these methods are briefly indicated in other chapters of this

book.) No pains must be spared in this part of the diagnosis, either by the clinician in his jealous care of materials to be saved for examination, or by the pathologist in the perseverance and ingenuity with which he undertakes their investigation; for it must be remembered that *nothing approaches in significance the isolation of the tubercle bacillus as a means of diagnosis of tuberculosis.* A few years ago this statement seemed the baldest truism; but to-day, when certain indirect methods of diagnosis have received very considerable attention, the paramount importance of the direct method needs to be emphasized. From much that is talked of certain of these indirect methods it might be thought that the actual demonstration of the bacillus was of no greater value than an investigation based upon the recognition of antibodies existing in the serum.

As regards the frequency with which the tubercle bacillus can be found in the circulating blood in cases of tuberculosis, there is some difference of opinion. Most authorities hold that, if cases of general tuberculosis be excluded, the bacillus can but rarely be demonstrated in blood films. At most a single bacillus is found here and there, after much searching, and often the morphology of such isolated bacilli is too dubious to bring much conviction to the observer's mind. Rosenberger in America and Forsyth in England have claimed that they can demonstrate tubercle bacilli in the blood in the majority of cases of phthisis examined. But other observers fail to confirm these results. The identification of isolated bacilli in films admits of much difficulty. The method of blood-culture described in chapter iii is unfortunately not available, because the tubercle bacillus grows so slowly in artificial media.

Assuming that no materials are available for examination, or that their examination has led only to negative results in regard to the causal bacillus, we turn to the indirect methods of diagnosis. The first of these indirect methods depends upon the employment of tuberculin, whereby a 'reaction' is given by a tuberculous but not by a non-tuberculous individual. One great advantage of this method of diagnosis is that it is easily within the scope of the practitioner. The second method is concerned with the opsonic index of the patient's blood to the tubercle bacillus.

### III. THE TUBERCULIN REACTION

If a minute quantity of 'old' tuberculin be injected into the subcutaneous tissue of a tuberculous person, a 'reaction' occurs which is of a very highly specific character. No such response is given by a non-tuberculous person. 'Old tuberculin is a syrupy brownish-yellow fluid, with a faint aromatic smell. It contains peptones and traces of other protein bodies, but the nature of the substance on which its extraordinary power depends is quite unknown. It is in a sense to be regarded as a toxin of the tubercle bacillus, but it is not a true toxin, like those of diphtheria and tetanus, since it is practically non-toxic for healthy animals or for man. Its injection in large quantity may cause a slight febrile reaction, but not much more than a similar injection of peptones, &c., from any other source. It differs, also, in a marked degree from the exo-toxins in that it is not destroyed by a temperature of 100°, or even of 120° C. It is dialyzable' (Emery). This 'old tuberculin' is the glycerine extract of tubercle bacilli which Koch originally introduced in a tentative manner for the treatment of phthisis and other forms of tuberculosis. Its administration for this purpose has for several years been almost

completely abandoned, the great use to which it is now put being in diagnosis. The tuberculin test may be employed in one or more of three ways: subcutaneously, cutaneously, and conjunctivally.

1. *The subcutaneous test* (Koch).

This mode of performing the tuberculin test is contra-indicated in patients who are febrile, and in those who are acutely ill by virtue of extensive or actively progressing lesions. In all other cases it is quite free from risks if carried out with due care, and is, in the writer's opinion, of greater value than either of the two methods to be described later.

The best method of performing the test is to administer an initial dose which is quite small. If no reaction follows this in forty-eight hours a second dose of double the size is given. If a slight reaction follows the first dose the same interval is allowed to elapse, and a dose *of the same size* is administered a second time. *If the response to a second dose of the same size is more marked than was the response to the first dose, this constitutes a positive reaction of great delicacy.* If no reaction follows either the first or the second dose, a third and still larger dose is given. If there is still no reaction the test may be considered to be negative; but some authorities give a fourth dose before arriving at this conclusion.

With regard to the actual size of the doses which it is advisable to choose, opinions differ. Some discretion must be exercised in respect of the extent of the lesion and whether it is deep-seated or capable of being kept under view during the stage of possible reaction. The writer's own practice in the majority of cases is to begin with 0·001 c.c. of the tuberculin (=1 milligramme), and to proceed to 0·002 c.c., 0·005 c.c., and 0·010 c.c., for the second, third, and fourth doses, observing the qualification mentioned above with regard to the value of an increase in the reaction as the result

of using a second dose of the same size. In infants and small children it is advisable to use doses which are one-tenth of these sizes. The practitioner may order a series of four doses of the above amounts, each of which will be diluted to 1 c.c. or to 10 minims of fluid, and sent by the dispenser in sealed glass ampoules for immediate use, a small amount of preservative being added. Or he may order a small quantity (say 2 c.c.) of the undiluted tuberculin, which will keep indefinitely in a stoppered bottle. By means of a 10 c.c. pipette, graduated to tenths of a c.c., he can make up the necessary dilutions as these are required, using a 0·5 per cent solution of carbolic acid as the diluting fluid. (To 9·9 c.c. of the diluting fluid add 0·1 c.c. of tuberculin ; mix ; label this ' Solution A '. 1 c.c. of this solution contains 0·01 c.c. of tuberculin. To 9 c.c. of the diluting fluid add 1 c.c. of ' Solution A ' ; mix ; label this ' Solution B '. 1 c.c. of solution B contains 0·001 c.c. of tuberculin.)

The actual procedure is as follows. The patient is, for preference, in bed during the application of the test; but this is not absolutely necessary. The temperature has been recorded on a four-hourly chart for at least two days prior to the test, and is found not to be raised above 99° F. For the convenience of the observation the injection is made in the early morning, so that two-hourly temperatures may be taken which should always include the sixth to the twelfth hour after the injection. The site of inoculation is not very important, but it is perhaps advisable to make it as near to the suspected tuberculous focus as practicable. In cases of suspected phthisis a convenient place is the region of the scapula. The usual aseptic precautions are observed with regard to the needle and the skin.

The ' reaction ' may be of two kinds, general and local.

(i) *The general reaction* includes a rise of temperature and

pulse rate, headache, and general malaise. The writer has occasionally observed a subnormal temperature with chilliness precede the febrile period. The raised temperature is the most valuable general sign of a positive reaction, because it is objective and can be measured. In most cases it occurs some time between the sixth and the twelfth hour after injection; but it may occasionally be delayed until later than the twelfth hour. A rise of more than half a degree

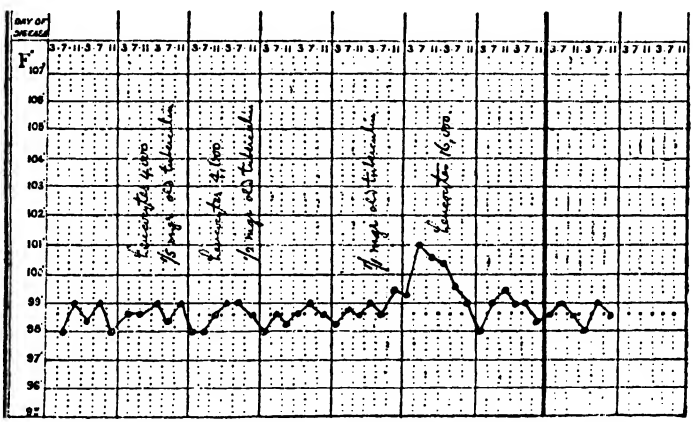


Fig. 6. Showing a positive reaction to old tuberculin given hypodermically.

must be regarded as evidence of a positive reaction if the initial dose be not larger than 0·001 c.c. in an adult; or at least it must be regarded as an indication for making the second dose of the same size as the first, for the reason already stated.

(ii) *The local reaction* is not always present as part of the response, or rather, is not always to be observed; but when it is present it constitutes a point of even greater positive value than the rise of temperature. The local reaction varies according to the site of the disease process. In phthisis it may show itself as increase of cough and pain in the chest. Tuberculous glands may become slightly more

swollen and tender. In cases of tuberculous peritonitis diarrhœa may occur. The writer once had the opportunity (needless to say it was not of his own choosing) of observing the local reaction in a tuberculous peritoneum, as this organ was examined by the surgeon during a positive tuberculin reaction. The sight was very remarkable. The lesion consisted of a mass of caseating tuberculous glands in the mesentery, with miliary tubercles in the adjacent peritoneum and considerable adhesion. When seen the peritoneum was of a vivid red colour, its vessels were engorged, and the lymphatics were very acutely inflamed. The temperature chart of this patient is appended (Fig. 6).

2. *The cutaneous test* (von Pirquet).

This method of examining a patient for the tuberculin reaction is very analogous to the performance of Jennerian vaccination for small-pox. The superficial layers of skin on the flexor surface of the upper arm are lightly scarified by a bayonet-shaped needle and a drop of a 25 per cent solution of old tuberculin is rubbed into the spot. It is advisable to make two control marks close by ; one of these is treated with the 0·5 per cent of carbolic acid in glycerin used to dilute the tuberculin, and the other is left without any sort of application at all. More recently von Pirquet has suggested the use of undiluted tuberculin, with a view to obtain more definiteness in the positive reaction. The writer has, in several cases, used three solutions—25, 50, and 100 per cent—at the same time and on the same patient, with the object of seeing if any quantitative results could be obtained. He found that if one solution gave a positive result all three did, and vice versa. When the test is positive the scarified area becomes rose-red in colour, slightly raised above the surface, and when the reaction is marked one or more vesicles may appear upon it. Around

the area there often develops a zone of fairly intense hyperæmia. During resolution there is usually a certain amount of desquamation from the scarified area, and a yellowish pigmentation marks the spot for a considerable time. These changes, as might be expected, are more delayed, and occupy a longer time, than those seen in the subcutaneous test. Moreover, they are not infrequently somewhat equivocal in character, leaving the observer in doubt as to whether the reaction is positive or negative. If no more reaction occurs in the area treated by tuberculin than in either or both of the control areas, the test is, of course, negative. This test is probably of much less value in adults than in children. A modification of von Pirquet's method has lately been introduced which depends upon applying the tuberculin in the form of an ointment. Of this method of using the test the writer has no experience.

3. *The conjunctival test* (Calmette).

The third method of applying the tuberculin test consists in inserting a drop of a 1·0 per cent solution of old tuberculin into the conjunctival sac of one eye. The other eye is regarded as the control. If a positive reaction ensues, changes commence in the mucous membrane after an interval varying from about six to twenty-four hours. It is customary to recognize three degrees in the reaction. The mildest degree consists of reddening of the caruncle and of the palpebral conjunctiva. The next degree of reaction shows these same changes more markedly and also enlargement of the vessels in the scleral conjunctiva. The third degree of response constitutes a genuine acute conjunctivitis, with exudation into the sac. In a few cases the reaction has been very intense, causing chemosis. The test cannot, therefore, be said to be devoid of some risk. It goes without saying that in observing the mild reactions

a close comparison of the two eyes must be made, and that a definite difference in vascularity is imperative before the test is regarded as positive. The same comment with regard to equivocal results applies to this test as to the cutaneous test.

*Comparison of the three tests.* After a good deal of experience of all three of these tuberculin tests the writer has come to the conclusion that neither the cutaneous nor the conjunctival approaches the subcutaneous test in its diagnostic value. As already remarked, the chief trouble with the second and third of these methods is in dealing with the not inconsiderable proportion of equivocal results, and the indecision that arises as to whether they are positive or negative. This difficulty, although not absent when the temperature is not quite steady, is rarely met with in the subcutaneous test, and when it occurs the observer has the power of giving a further and larger dose of tuberculin to settle the doubt. But in addition to this advantage of the subcutaneous test, the writer holds that it is more constant in its results than is either of the other methods; that is, it is more often positive in tuberculous patients and less often positive in non-tuberculous patients. An actual comparison of the relative value of the tests can be made by employing any two or all three of them *at the same time* in the same patient. The writer has seen a definite positive reaction given to the subcutaneous test in a case of phthisis, in which Calmette's test was negative and von Pirquet's test doubtful. The patient, an adult, was admitted to the Great Northern Hospital with acute bronchopneumonia and hæmaturia. Calmette's and von Pirquet's tests were both performed on the same day, with negative results. A week later, the temperature being normal, the subcutaneous test was undertaken, and a marked positive

reaction was obtained. Three weeks later the physical signs in the lungs focused down to both apices, and a little sputum appeared, which contained tubercle bacilli.

### IV. THE TUBERCULO-OPSONIC INDEX.

The 'opsonic index' of the blood to the tubercle bacillus is by some authorities held to be so constant in non-tuberculous subjects that any marked deviation from the normal (regarded as unity) is by them considered to be good evidence of tuberculous infection. It seems certain, however, that such a conclusion should not be based, as it often is, upon a single examination, but that a series of indices should be taken. This method is not within the scope of the practitioner, who, if he desires this particular investigation, should send specimens of blood in sealed pipettes, duly labelled, to a pathologist well versed in the special technique of opsonic work.

### V. THE SPECIFIC TREATMENT OF TUBERCULOSIS

Although anti-tuberculous sera have been introduced by Marmorek and others, the only form of specific treatment at all widely adopted is by means of tuberculin. In England the material most frequently used for the purpose is Koch's new tuberculin (T. R.). At present there exist considerable differences of opinion both in the choice of cases to submit to the treatment, and in the choice of time and size of dose. Most authorities agree that it is inadvisable to give tuberculin to patients who are markedly febrile, or who show much oscillation in temperature and in general condition. There is also a consensus of opinion that no patient should be started upon a course of tuberculin treatment immediately he comes under observation. The best cases to select for specific treatment are undoubtedly

those in whom there has been produced, as the result of non-specific measures, some definite retrogressive changes in the tuberculous lesions (see p. 180). In such cases the use of small doses of tuberculin appears to act beneficially by stimulating specific resistance and hastening the processes of healing. These considerations do not take into account those experimental efforts made to check the course of a rapidly progressive and desperate form of tuberculosis which shows no response at all to other modes of treatment. Such efforts, upon rare occasions, seem to be fraught with success; and the most that can be said against them is that they are usually doomed to disappointment.

As regards the size of dose of tuberculin, and the frequency of its administration, there is, as already said, no rule to follow. Seeing that some workers employ what appear to the writer unnecessarily heroic doses, and others give doses that seem unnecessarily minute, yet both claim good results, it would appear reasonable to strike a middle course, and this is probably what most practitioners do. It is probably of no service in the treatment to aim at a reaction to the dose of tuberculin employed. A dose of $\frac{1}{20000}$ mgr. may well be given as the first dose, repeated with ten days' interval, until four doses are given. A second series of four doses of $\frac{1}{10000}$ mgr. may follow, observing the same intervals. And so on, advancing by $\frac{1}{10000}$ mgr. at every fifth dose. Should any dose be followed by a reaction, local or general, or by a rise of temperature without other evidence of reaction, the dose should be no further increased for a while. (For the use of tuberculin by mouth see p. 174.)

# CHAPTER XIV

## ON CERTAIN SPECIFIC SERUM TESTS AND THEIR VALUE IN DIAGNOSIS

THE diagnosis of disease has during recent years received great assistance from the discovery of certain interactions that are demonstrable between the blood serum and other body fluids on the one hand, and the infective agent causing the disease on the other. Although in none of these instances has the principle existing in the serum, and upon which the interaction turns, been isolated as a definitive substance, there are reasons for knowing that infected serum contains a number of such principles, each possessing different properties. In the present stage of our knowledge it would perhaps be more fitting to speak of these hypothetical substances as properties of the serum than as substances existing in it; but custom favours a nomenclature which conceives of these properties as residing in actual material ingredients of the serum. The various principles that are formed in the body fluids as the result of their invasion by bacteria are termed *Antibodies*. The name is a convenient one, but has the objection that it carries a suggestion that these substances necessarily fulfil some function in the defence of the body against micro-organisms. Of this, however, the evidence is far from being complete, and such a teleological view of the situation is open to much criticism. Moreover it is highly probable that certain of these properties of the serum are only developed after the blood is shed from the body, so that, valuable as their recognition may be for

purposes of diagnosis *in vitro*, it by no means follows that they have any protective function *in vivo*.

It is quite impossible to say exactly how many of these antibodies have their existence established with certainty; for it is highly probable that in the present somewhat rudimentary state of the science of Immunity different observers have given different names to the same principle. The point of view of different experimenters being also different, their results are not comparable. It is very significant that with the multitude of isolated observations that have accumulated in this branch of pathology during recent times, a practical application of them to the actual mechanism of the immune process as it takes place in the body seems at present quite impossible. Of bricks and mortar there is an abundance, a superfluity it would almost seem, but the edifice as yet scarcely begins to rise. It seems as though the plan of the building up till now has been hidden. The discovery of the isolated facts above mentioned is, of course, a matter of great importance; but even here the practical outcome is very often not the direct application of the fact to the solution of the main problem, so much as an indirect use of the fact for a purpose not considered at all when the research was originated. With an eye fixed upon a larger horizon which he does not reach, the student of Immunity wanders into a nearer by-path which nevertheless amply rewards his efforts. Not infrequently, having made a discovery which is of great practical value, he is bound to confess that, instead of being a rational outcome of his previous labours, it is but an empirical addition to his knowledge which he has accidentally stumbled against.

The variety of antibodies produced during the operation of a micro-organism depends upon the nature of the infecting

agent and upon the kind of response made by the patient to infection by it; and the art of pathological diagnosis by means of specific tests turns upon devising means whereby the presence of certain dominant antibodies can be demonstrated in the tissue fluids of the patient. It is proposed to deal in this chapter with diagnostic serum tests which have, up to date, the weight of authority and experience to recommend them. For convenience of description these tests fall under two headings, according as the antibody concerned is the substance termed *Agglutinin* or *Immune body*.

## I. THE AGGLUTINATION TEST

### (THE WIDAL TEST)

Agglutinins are substances which possess the power of 'clumping' the specific bacteria which have led to their formation in the tissue fluids. This diagnostic principle was first applied by Widal to the serum of patients suspected to be suffering from typhoid fever, following the demonstration of the agglutination phenomenon by Gruber and by Durham. It is in its relation to typhoid fever that most of the observations in connexion with the test have been made. So valuable has the test now become that its importance can scarcely be overestimated. The test is also applicable to the diagnosis of paratyphoid fever, to Gaertner bacillus poisoning, to Malta fever, to cholera, and to bacillary dysentery. These diseases are not the only ones against the causal microbes of which the body elaborates agglutinins. These antibodies are probably formed as a response to most infecting bacteria; but in other instances than the above the amount of the substance formed is too small to enable a practical demonstration of its presence to be made, or the morphology of the causal micro-organism is unsuited

to the test. As an illustration of the latter may be mentioned the pathogenic cocci, which possess an inherent tendency to clump of themselves, and are withal non-motile. Agglutination tests employed with the object of diagnosing coccal infections do not therefore appear to be of much service.

1. *Typhoid fever.*

As very few practitioners are able to keep a culture of *B. typhosus* as part of their laboratory equipment, the procedure from their point of view is extremely simple. It consists of pricking the patient's finger or ear, drawing up about 20 c.m. of blood into a glass pipette, sealing the ends of the pipette in the flame, and forwarding the specimen to the pathologist. Upon its arrival at the laboratory the pathologist dilutes the serum, which has separated from the clot, by the addition of known quantities of normal salt solution. This diluted serum is then intimately mixed with a recent culture of typhoid bacilli, and a hanging-drop preparation of the mixture is put up for microscopic examination. Two control specimens are put up side by side with the test specimen. The first control consists of the typhoid culture mixed with diluted serum from a person who is known not to have had typhoid fever nor to have been inoculated against the disease. The second control consists of the typhoid culture mixed with normal salt solution only. If the test be positive the actively motile bacilli become slowly paralysed, and are then seen to group themselves together in large clumps, leaving no scattered bacilli anywhere in the field. In both of the controls the bacilli remain actively motile and are uniformly distributed over the field.

This is the microscopic method of performing the test, and it is the method most in vogue. Some pathologists

prefer the macroscopic method, making the necessary dilutions in greater bulk, incubating the mixture of diluted serum and bacillary emulsion in a sealed glass tube and noting the presence or absence of sedimentation at the end of a given time. Controls are, of course, again used.

Since it has been found that the bacilli need not be living in order that agglutination shall take place, it is open to the practitioner to perform the test himself, using a dead culture of typhoid bacilli. But the absence of motility does away with one of the most characteristic parts of the interaction of serum and bacilli, and for this reason, and because it is much more difficult to obtain an emulsion of dead bacilli which is free from small clumps to begin with, the test with dead micro-organisms is not so delicate as with the living culture.

The agglutination test is a *relative* pathological test (see p. 6). It is specific, but only quantitatively so. It depends for its value upon an arbitrary selection of limitations in regard to the degree of dilution of the serum, the time during which the test is allowed to continue, and the completeness or otherwise of the interaction. A proper report to the clinician should contain a reference to these points, since there is no universal rule with regard to them. Conditions which satisfy one pathologist do not satisfy another, and (within limits) the more fastidious of two pathologists will prove the safer guide. The practitioner may be inclined to accept as positive, in a case showing certain clinical evidences of typhoid fever, a partial interaction which in another case, showing no such evidence, he would regard as negative. He therefore needs to be told how delicate the test has been made in the laboratory. The conventions with regard to the above points need never be rigidly chosen. There should, however, be a minimum set

of requirements which are to be fulfilled if the test is to be regarded as positive. These requirements are as follows :—

(i) The dilution of the serum should be 1 in 20 at least.

(ii) The time of the test should not exceed one hour in the warm incubator.

(iii) The interaction should be 'complete', i.e. all bacilli should be motionless and should be clumped.

(iv) Needless to say, neither of the controls should show any clumping. In actual practice the pathologist, if he finds these minimum requirements are fulfilled, will proceed with dilutions of the serum of 1 in 40, 1 in 80, 1 in 160, &c., until he defines the upper limits of the test. He is then able to give a much more convincing report. Emery lays stress upon the occasional occurrence of agglutination with high dilutions of the serum in cases where there is no clumping with low dilutions, and this unusual phenomenon (which the writer has not himself observed) must consequently be borne in mind by the pathologist.

In the interpretation of results the following facts must be taken into account.

(i) The test is rarely positive during the first week of the disease, and scarcely ever before the fifth day. During the first week, before the development of agglutinin, the diagnosis of typhoid fever, so far as laboratory methods are concerned, turns upon the isolation of the bacillus from the blood (see p. 24) or from the stools. Fortunately for purposes of diagnosis, positive blood-cultures are yielded in the great majority of cases during the very period when agglutinin is absent (first week). The importance of a leucopœnia during this same period is also to be remembered (see p. 48).

(ii) The most convincing of all positive reports is that which records a rise in the amount of agglutinin present in

the serum, the test showing clumping to occur with a higher dilution upon one day than upon a previous day.

(iii) A positive test may mean that the patient has had typhoid fever at some former occasion, not that his present disease is of this nature. The agglutination interaction may persist for any time up to five years after an attack of typhoid fever. It persists somewhat longer in women than in men. Demonstrable increase in the degree of agglutination from day to day or from week to week proves that *this* attack is typhoid fever.

(iv) In a few cases of typhoid fever agglutination does not occur until defervescence has commenced, and in a few instances it does not occur at all.

(v) The test is occasionally positive, on the basis of the above-mentioned minimal requirements, in diseases which are not typhoid fever. (But note iii in this connexion.)

(vi) It sometimes happens that the test is positive with one strain of typhoid bacillus and negative with another. If, therefore, the clinical evidence is strongly in favour of the diagnosis of typhoid fever, the test must be performed with more than one strain of bacillus. Strange though this appears, the writer has known the test to be negative when the bacillus used has been that obtained from the patient by blood-culture, and positive when a laboratory strain has been employed.

2. *Paratyphoid fever.*

It is now generally recognized that *B. typhosus* is not the only member of the coliform group of micro-organisms which causes acute enteritis of a specific infective form. Other members of the group have been shown to be at times intensely pathogenic, and have been isolated from individual cases of acute enteritis, and from epidemic cases. Sometimes the illness resembles true typhoid fever very

closely, but the causal microbe differs from *B. typhosus* in certain of its characters, and the serum of the patient fails to agglutinate the typhoid bacillus. Such cases are termed Paratyphoid or Paracolon fever. Of these pathogenic paratyphoid bacilli two members have been isolated with sufficient frequency to justify their provisional recognition as specific. They have been called paratyphoid A and paratyphoid B, and the two strains are often kept in pathological laboratories for the purpose of applying Widal's test in the event of the serum of a case of enteritis suspected to be typhoid fever not clumping *B. typhosus*.

3. *Gaertner bacillus disease.*

In another set of cases of acute enteritis, not seldom occurring in small epidemics, the disease runs a much shorter course than in typhoid fever—even as short as forty-eight hours—has a very brief incubation period, and the causal bacillus, when isolated, is again found to belong to the Coliform group but to possess characters which differentiate it from *B. typhosus*. Agglutination with typical *B. typhosus* is again absent. One such pathogenic micro-organism was originally isolated by Gaertner, and is hence called by this observer's name. Outbreaks of 'food poisoning' are not infrequently traceable to this source. Klein holds that the early acute intestinal symptoms of brief duration which sometimes occur from ten to fourteen days before the onset of typhoid fever, are due to infection by this micro-organism. As might be expected, agglutination of Gaertner's bacillus by the serum of affected patients—a valuable help in diagnosis—does not persist nearly as long as agglutination of Eberth's bacillus by the serum of typhoid patients. In an epidemic of Gaertner poisoning investigated by Dr. English and the writer, in which twenty-one girls out of thirty were affected in a rescue home, it was found

that even in the most severe cases Widal's test, from being definitely positive, rather suddenly became negative two weeks after the illness. The bacillus used for the test was obtained from the heart's blood, spleen, and liver of a fatal case.

4. *B. coli infections.*

Sporadic cases of acute intestinal infection by *B. coli* are not uncommon, and the only means of identifying the causal member of the group may be by carrying out Widal's test with the patient's serum and several colonies in turn of the bacilli isolated from the stools. By this means the specific strain may be identified, and an appropriate vaccine may be prepared for treatment.

A 'group reaction' may be shown in these cases, partial clumping being obtained with the typhoid bacillus. This fact emphasizes the necessity of observing the 'minimum requirements' already referred to in performing Widal's test.

If the infection is of the urinary tract, peritoneum, or other part of the body, and the bacillus can be isolated, the test is not required; but the absence of agglutination in any acute case showing constitutional symptoms is presumptive evidence against the bacillus isolated being the sole cause of the illness.

5. *Malta fever.*

Widal's test is of great value in the diagnosis of Malta fever, and especially in chronic or latent cases in which blood-cultures may prove to be sterile. Provided that the controls are negative, complete agglutination of the *M. melitensis* by serum of dilution 1 in 30 in half an hour is to be taken as a positive test in any case giving clinical evidence of the disease. The agglutination, however, is in many instances quite marked with much higher dilutions than this.

6. *Cholera.*

It should be noted that the order of Widal's test may be reversed. Instead of using a laboratory culture of the suspected micro-organism and the patient's serum, a micro-organism of doubtful nature obtained from the patient may be investigated by use of a serum known to be immunized against certain bacteria. This order of employing the test is illustrated in the diagnosis of cholera. Here, again, the value of Widal's test is very high. It may even be carried out with the mucus from a suspected stool, without isolation of the vibrio by culture. For this purpose a commercial immune serum is employed, and a hanging-drop specimen is made direct from the fæces. If the patient is suffering from cholera, clumping will occur, sometimes with a dilution as high as 1 in 10,000.

A similar use of Widal's test to that described in the last paragraph may be made when a coliform bacillus is obtained from a patient's blood, or urine, or fæces, or elsewhere. Diluted serum from a known case of typhoid fever, or from an animal recently immunized by injections of *B. typhosus*, is mixed with the bacillus under investigation, and agglutination is tested for. In this way time is gained in establishing the diagnosis, which may later be confirmed by the routine set of bio-chemical reactions in use in the laboratory for the identification of *B. typhosus*.

## II. THE IMMUNE BODY TEST

### (THE WASSERMANN TEST)

This test is generally spoken of as *the fixation of complement*. It was originally applied by Wassermann to the diagnosis of syphilis, following certain experimental researches conducted by Bordet and Gengou. As a consideration of the test involves the use of certain terms not hitherto used

in these pages, a brief digression must be made for the purpose of clearing the ground.

To the various foreign substances of an organic nature which have been introduced from time to time into the animal body for purposes of research—whether bacteria, their endo-toxins or exo-toxins, tissue-cells, blood-corpuscles, &c.—the term *antigen* has been applied. The repeated injection of small doses of an antigen usually results in a certain degree of immunity on the part of the animal to the further injection of that substance. This immunity is apparently brought about by the interaction of three substances : (1) *the antigen*, (2) *the immune body*, an antibody produced by the repeated operation of the antigen, and (3) *complement*, a substance residing normally in the animal's blood. These three substances together constitute 'an immune system'. The immune body links the antigen to the complement, and thus neutralizes the effect of the foreign substance upon the animal. This property possessed by the immune body of linking antigen to complement has given rise to its synonym *amboceptor*. When this process of linking complement to antigen takes place the complement is said to be 'fixed'. The immune body is specific in its action and can only combine with its co-related antigen. Complement, however, is not specific, and is capable of exercising its function in connexion with any kind of immune body and with any antigen that is co-related to such immune body. The immune body is thermo-stable, and is not lost to the serum when this is heated to 55° C. for half an hour. Complement is thermo-labile, and is destroyed by such heating. Serum thus treated, and losing its complement, is said to be 'inactivated'.

With this preface it is possible to enter upon the rationale

of Wassermann's test for the presence of immune body by fixation of complement.

Consider the effect of injecting a rabbit with the red blood-corpuscles (antigen) of a sheep. An immune body is formed by the rabbit, and this, together with complement existing in the rabbit's blood, causes hæmolysis when the rabbit's serum, containing these two ingredients, is brought into contact with a suspension of sheep's red blood-corpuscles in a neutral fluid. These three substances, sheep's corpuscles, immune body, and complement, constitute a 'hæmolytic system'. If the rabbit's serum is heated before being mixed with the sheep's corpuscles, and the serum is thus inactivated, hæmolysis does not take place.

Consider now that this inactivated hæmolytic serum and the sheep's red blood-cells are mixed together. The result will be an incomplete hæmolytic system. Call this system A. Consider also that the elements of another immune system are mixed, which system is complete if it contains immune body, but is not complete if it does not contain immune body. Thus, this second system consists of antigen, (?) immune body, and complement. Call this system B. If now these two systems are mixed together, the result will differ according as system B is complete or incomplete. If it be complete, that is, if it contain immune body, the complement in this system is already 'fixed' by the immune body to the antigen, and therefore no complement is available for the completion of system A. System A therefore remains an incomplete hæmolytic system; no hæmolysis occurs, the solution formed by the mixture of A and B remains clear, the red cells sinking to the bottom of the tube. *As a test for immune body in system B the test is positive.* But if system B be incomplete, that is, if it contain no immune body, the complement in this system is not fixed to the

antigen but is available for completing system A, which now (complement not being specific) becomes a complete hæmolytic system ; hæmolysis occurs, the solution formed by the mixture of A and B no longer remains clear, but the hæmoglobin of the red cells diffuses into it. *As a test for immune body in system B the test is negative.*

It has already been noted that immune body is specific. It follows, therefore, that a test for immune body is also a test for the antigen which has led to the production of the immune body—just as a test for agglutinin is a test for the antigen which has led to the production of this form of antibody.

To take a practical illustration : consider the Wassermann test applied to a suspected case of typhoid fever. (In actual practice the agglutination test is far simpler ; but the immune body test has been observed to be positive in cases in which agglutination has been absent.) The procedure will be as follows :—

*For incomplete hæmolytic system A.* Add inactivated hæmolytic serum (immune body) of a rabbit to a suspension of red blood-cells (antigen) against which the serum had been hæmolysed.

*For* (*? complete* / *? incomplete*) *immune system B.* Add filtered broth culture of typhoid bacilli (antigen) and inactivated serum of a suspected case of typhoid fever (? immune body) to fresh guinea-pig's [1] serum (complement).

Mix systems A and B and incubate the mixture. If the case is one of typhoid fever, and immune body is present in the serum of the patient, the complement is fixed to the antigen by this immune body, and system B is complete. System A therefore remains incomplete ; no hæmolysis

[1] The guinea-pig is chosen because its blood is very rich in complement.

occurs ; the test is positive. If the case is not one of typhoid fever there is no typhoid immune body in the serum, the complement present in system B is free to interact with the antigen and immune body of system A, which is now complete ; hæmolysis takes place ; the test is negative.

The principle of Wassermann's test has been successfully applied to several diseases other than typhoid fever. The disease in connexion with which it has been most extensively studied, and in the diagnosis of which it is rapidly taking a most important place, is *Syphilis*. The causal microbe of this disease (*Spirochæta pallida*) cannot yet be grown outside the body on artificial media, or certainly cannot yet be grown in such a way as to provide a pure bacterial antigen wherewith to conduct the test. The pathologist therefore falls back for antigen upon an emulsion of liver tissue from a case of congenital syphilis examined in the post-mortem room, or upon the tissues of a syphilitic fœtus.

The above sketch of the steps in the performance of Wassermann's test gives no idea of the actual technique observed, nor of the care which it is necessary for the pathologist to observe in order to obtain accuracy of results.

As in all pathological 'tests', the reaction is only quantitatively specific. In other words, to make the test of service, certain conventions in the way of dilutions are necessary, and it is the careful observance of these conventions, with the rigid use of controls, that makes the test somewhat tedious and confines it to the practice of the expert.

This brief sketch of the Wassermann test is given here solely in order that the practitioner may understand the principle underlying the test. As may be readily gathered, the test is at present altogether beyond the powers of the clinician, and necessitates exact laboratory methods. In any case in which the diagnosis of syphilis or of parasyphilitic

disease is indicated, the practitioner collects blood from the patient, seals it in a glass pipette, and forwards it to the pathologist. A liberal amount of blood should be sent, not less than one cubic centimetre.

*The results obtained* up to the present have been most helpful and encouraging. It is probable that at least 90 per cent of patients whose tissues have at some time or other been impregnated with the virus of syphilis give a positive reaction. In addition to diagnosis, the question of the duration of treatment receives considerable help from the test. By its aid the practitioner is able to decide the time at which he may safely suspend his antisyphilitic remedies: a negative reaction indicates that the tissues are free from the virus. Several interesting facts have been established in connexion with the ætiology of diseases. The prevalence of syphilis as a causal factor in diseases of the aorta and aortic valves is borne out by finding that a considerable percentage of patients suffering from these affections give a positive Wassermann test. It is worthy of note, on the other hand, that of patients with mitral affections only a small number give a positive reaction.

# CHAPTER XV

## FEVER WITHOUT OTHER PHYSICAL SIGNS

### (A STUDY IN CLINICAL AND PATHOLOGICAL METHODS)

In a large number of cases of disease in which clinical pathology gives assistance in diagnosis *fever* plays a conspicuous part. When 'physical signs' are absent the investigation of a case of fever becomes in large measure an exercise in pathological methods. It is proposed to deal with such cases in this chapter, and it has been thought well not to omit clinical details when these are important in the elucidation of the subject.

Cases of fever fall rather naturally into two groups. In the first group certain physical signs more or less adequate to the diagnosis are elicited by examination of the patient; in the second group no such signs are obtained. An intermediate group of cases exists in which there are physical signs, but they are signs inadequate for diagnosis—ambiguous signs, admitting of more than one interpretation. The rose-spots of typhoid fever constitute an adequate sign, pathognomonic of the disease; enlargement of the spleen is an ambiguous sign, which, though indicating the possibility of typhoid fever, may be caused by many other infective processes. Seeing that this intermediate group of cases of fever demands further investigation for the purpose of diagnosis, it belongs more strictly to the second than to the first group.

In the second group of febrile patients, who present no physical signs, or only present signs that are equivocal as regards diagnosis, there are found many cases which tax

the resources of the physician to the utmost. Indeed, these cases include some of the most difficult, yet fascinating, problems of clinical medicine. On reflection it will be found that such cases of fever are concerned with lesions of an infective nature, situated in organs or tissues more or less deep-seated, which yield signs less readily than organs placed superficially. Such organs or tissues are the blood, the intestines, the gall-bladder, the pelvis of the kidney, the pancreas, the endocardium, the spinal meninges.

The cases may be divided into two groups, according as the physical signs are latent or difficult to find, or are altogether absent.

### I. PHYSICAL SIGNS OVERLOOKED OR LATENT

1. *Cholecystitis.* A not uncommon cause of fever without obvious signs. The patients are usually the subjects of gall-stones, but this is not always so. Often they are stout, making abdominal examination difficult. Pain is generally present, though it is often by no means severe ; sometimes it is absent. Colic is not a feature of the disease. Flatulent distension of the bowels is almost constant. The attacks are prone to recur, sometimes after brief intervals, and the course of the disease may then suggest the occurrence of typhoid fever, or of Malta fever, with relapses. Repeated palpation may discover a rounded elastic tumour in the right hypochondrium, and in this discovery the genu-pectoral position may give valuable help. This tumour may only be felt for a brief period in the course of the disease. The urine should be tested for traces of bile, for it should be remembered that the urine may be icteric before any jaundice is noticed in the skin or mucous membranes. Jaundice may be absent throughout the whole course of the disease. Even with an intermitting type of fever and with

the occurrence of rigors the inflammation is not necessarily suppurative. And there may be no leucocytosis ; indeed, the writer has in four cases found the leucocyte count to be low (4,000–6,000), another fact which may suggest the presence of typhoid fever or Malta fever.

2. *Pyelo-cystitis.* In some cases of infection of the urinary tract the amount of pus in the urine may be quite small ; and what is not seldom the sole sign of the disease may thus be easily overlooked. Sudden rises of temperature, often accompanied by rigors, in old men, or in patients suffering from diseases of the nervous system leading to sphincter troubles, frequently have their explanation in infections of the urinary tract. By far the commonest micro-organism at work is *B. coli*, admitting of ready isolation from the urine (see p. 117).

3. *Pyorrhœa alveolaris.* A close inspection of the teeth and gums should never be omitted in cases of fever of obscure origin. Long-continued and marked pyrexia may certainly own no other cause than oral sepsis. The form of the fever is apt to be periodic, with intermissions lasting from one to several days. The fever took this form over a period of many weeks in the most severe instance of the disease that the writer has ever seen (see p. 111).

4. *Perigastritis and subphrenic abscess.* Serious complications of gastric ulcer, physical signs being ofttimes delayed, perhaps for a fortnight or more. When signs do appear pleural friction is apt to be the first. The same conditions may follow gastro-enterostomy, or the suture of a perforated gastric or duodenal ulcer. A rising leucocyte count may suggest to the observer the actual sequence of events (see p. 46).

5. The subjects of *acute rheumatism* are prone to develop bouts of fever with little or nothing manifest in the way

of physical signs. The administration of sodium salicylate may have no effect upon the fever. It is highly probable that in these cases some serous membrane is in a state of smouldering inflammation. But signs of the inflammation may not be forthcoming for one or more of these reasons: the presence of old valvular disease may make the diagnosis of a recurrence of acute endocarditis impossible; pericardial adhesion, ofttimes universal, prevents the appearance of the physical sign of pericarditis; and of acute myocardial disease there is no physical sign. The undoubted occurrence of rheumatic pleurisy and rheumatic peritonitis must not be overlooked. These cases of rheumatic pyrexia, not seldom considerably prolonged, are always a source of anxiety to the physician, and the anxiety is of necessity increased in the presence of valvular disease. For the transition from simple rheumatic endocarditis to that malignant type of endocarditis in which streptococci play so important and so fatal a part may be very gradual and may deceive the very elect. However, a careful search for the cardinal signs of infective endocarditis, which includes bacteriological cultivation of the blood, will generally lead to a prognosis which future events will justify. The concurrence of chorea, or of nodules, is much in favour of the non-infective variety of the disease, though neither event quite excludes streptococcal endocarditis (see p. 16).

6. *Localized tuberculosis* is probably the commonest cause of fever with latent physical signs, or with signs that are difficult to elicit. There is sometimes a too ready tendency to conclude that a patient is tuberculous because he is found to be febrile over a lengthy period, and this conclusion should be resisted until several other causes that are more easily excluded have been passed in review. Nevertheless the possibility of the disease must always be borne in mind,

and it is useful to remember certain situations where this infection is apt to lead to more or less disturbance of general health with fever, usually mild and remittent. These situations include the lung, the pleura, the peritoneum, the lymphatic glands, the kidney and suprarenals, the Fallopian tubes, and the spine. Critical examination of all these organs and their functions must be made, and one or other of the tuberculin tests must be undertaken, remembering the limitations which the presence of fever imposes upon these last-named investigations. It occasionally happens that there comes under observation a febrile patient who, in the past, has given demonstrable proof of active tuberculosis: this must be allowed great weight in the present search for the cause of the fever. The frequency of secondary pyogenetic infections in tuberculosis must also be remembered; such a secondary infection may occasionally be demonstrated by blood-culture.

7. *Fever following surgical operations.* A physician is not infrequently called upon to discover the cause of pyrexia arising in a patient shortly after an operation has been performed. In such a case, however confident (and justifiably so) the surgeon may be of his technique, it must never be forgotten that his wound constitutes a physical sign which must be closely scrutinized. Painful experience has at length taught the modern surgeon to treat with due respect the subtle possibilities of the pyogenetic coccus. He has been for some years past scrupulously careful of his hands, of his instruments, and of the patient's skin and mucous surfaces. To these cautions he has in recent times added others: he no longer holds close converse with his assistant at a distance of a few inches from the open wound, but covers his mouth and nose with sterilized gauze, which filters his breath from all particulate matter. His hair is

similarly protected from contaminating the wound, and his hands are sheathed in rubber gloves. The care with which he prevents the entry of micro-organisms seems almost to have reached the limits of practical surgery. Might he not now with advantage turn his attention to greater care for the integrity of the tissues through which he passes during the steps of his operation ? That is to say, might he not be repaid for showing more respect to the soil, as he has been repaid for showing more respect to the microbe ? Along this line also something has recently been gained : strong chemicals that cause acute inflammation or actual sloughing are now rarely applied to the skin area chosen for operation, as they were wont to be, several hours previously ; delicate adhesions and useful fibrinous exudates are no longer disturbed ; retractors are constructed with some idea of avoiding bruising in their use. But there is a great deal still to accomplish, and that surgeon's results will be best who constantly reminds himself that contused and ischæmic tissues form an excellent nidus for microbic invasion. The skill with which anæsthetics are now given tempts many surgeons to more deliberation in their work than is actually necessary for the purpose in hand. No doubt the many wounds that healed by first intention in the pre-anæsthetic days owed their success to the rapidity of the operator, rendered imperative by the difficulties under which he laboured. There was little time either for damaging the tissues or for collecting bacteria in the wound.

These considerations prevent any feeling of surprise, however disappointing the event may be to the surgeon, when occasional suppuration is found to be the cause of post-operative fever. It is right that the lungs, heart, and other organs should be thoroughly examined ; that the

possibility of malaria and influenza should be discussed; that a number of other things should be duly borne in mind. But most surgeons know too well the limitations of their art. They realize the ubiquity of the pyogenetic microbe, and they recognize that when raw tissues lie exposed to the air for a long time, as they occasionally must do, when a residual collection of blood-clot is inevitable, or when an operation is performed hurriedly and under adverse conditions—that in any of these circumstances suppuration is no disgrace, though the absence of it is good fortune. If fever occur after an operation, provided the rise of temperature be not trivial or transitory, the sooner the wound is examined the better. If the leucocyte count is found to be rising the examination should be made at once. Cultures should be taken from any fluid present, be it 'blood-stained fluid', 'serum', or obvious pus, and efficient drainage ensured. If a growth of any micro-organism is obtained from the cultures an appropriate vaccine should be prepared and administered forthwith (see p. 187).

## II. PHYSICAL SIGNS ENTIRELY ABSENT

1. *Influenza* is probably the commonest cause of a pyrexia without other physical signs. Indeed, most cases of influenza run their course without other signs than that recorded by the thermometer. Hence the doubt which always exists in the mind of the physician as to the accuracy of his diagnosis; for there is nothing specific about any of the symptoms of influenza, nor about all of them taken together; they do but spell acute microbic poisoning. This doubt is naturally less, and may justifiably be quite absent, at the time of an epidemic. The fever in uncomplicated cases is usually over by the fifth or sixth day; if it lasts longer than this there is

a high degree of probability that some complication is present, or that the disease is not influenza. If a complication exists a focus of infection is probably present (bronchial, pulmonary, intestinal, biliary, endocardial, meningeal, &c.) and physical signs are usually forthcoming. In uncomplicated cases a leucopœnia is of great service in diagnosis, especially in the absence of the typhoid agglutination reaction. Even with pulmonary complications, provided the infection remains pure, a leucopœnia is apt to occur. But in the experience of the writer a mixed infection, especially with the pneumococcus, is the rule in influenzal pneumonia, whether lobar or lobular, and a high leucocyte count is therefore by no means uncommon. Despite some earlier statements to the contrary, it seems that in uncomplicated influenza the causal microbe is rarely if ever demonstrable in the blood-stream. Certainly by culture it has not hitherto been demonstrated. In influenzal endocarditis the writer was able to cultivate the bacillus from the blood in 1904, and this experience has been repeated several times since. The bacillus has also been isolated recently from the blood-stream in a case of influenzal phlebitis by Dr. Thursfield.

2. *Typhoid fever* is undoubtedly the most frequent and the most important cause of fever of longer duration than five days in Great Britain, physical signs being absent. As a possible cause of any case of obscure pyrexia it must be perpetually borne in mind. Neither a sudden form of onset, nor absence of headache, nor variations from the customary form of the temperature chart, nor an alleged immunity from the disease in the particular locality in which the patient chances to reside, nor any one of several other things that are sometimes adduced as evidence against typhoid fever, must be allowed to interfere with a consideration of this infection as a possible cause of pyrexia.

Diarrhœa is no longer regarded as an almost essential symptom, and often no inquiry is made nowadays even concerning epistaxis. But there is still, with some, a reluctance to investigate a case of fever from this point of view unless certain cardinal features present themselves. The truth is, the manifestations of the disease are so protean that safety only lies, as already said, in regarding every patient suffering from fever of undetermined cause as a suspect. Mention has been made of the acute onset occasionally seen in typhoid fever; in one case of this kind, seen with Dr. Kempe, of Salisbury, the first symptom was acute delirium, which continued during the first fortnight of the disease; there was no headache at any time. Both in this case and in another case of typhoid fever with marked delirium during the invasion period there was a strong neuropathic family history. Before the immunity of any district from typhoid fever be accepted as evidence against the disease in any particular case information must be forthcoming that the patient was continuously in that district during the two weeks but one preceding the onset of the illness; for the infection may have occurred during a temporary sojourn elsewhere. In one instance of this kind it was found on reference to dates that the patient, then residing near Epsom, left Ems, where she had been living on a milk diet and drinking the waters, exactly fourteen days before the first day of the illness. In another case, occurring in a city boasting a very clean bill of health in regard to typhoid fever, it was found that a week-end had been spent in another city in which typhoid fever is endemic, and that this brief holiday occurred twelve days before the acute onset of the disease.

In the pathological investigation of a possible case of typhoid fever sufficient importance is often not attached to the leucocyte count. The agglutination test should

always receive this support, for the association of a leucopœnia with even a partially complete Widal reaction is a valuable indication of typhoid fever. A complete Widal reaction with a leucopœnia may be taken as diagnostic. If the agglutination reaction is not present, as it may not be during the first week of the disease, the diagnosis may often be established by blood-culture, the typhoid bacillus being isolated from the circulation. Allied to typhoid fever, and often undistinguishable from it clinically, are the cases termed paratyphoid or paracolon fever. These cases are even more liable than cases of true typhoid to present no physical signs. The diagnosis can only be made with certainty by isolation of the micro-organism from the blood-stream, from the urine, or from the fæces (see p. 144).

3. Certain cases of *Septicæmia*, and especially septicæmia in the puerperium, may lead to marked fever without other signs. The most careful obstetrician may fail to discover aught amiss with the pelvic viscera; indeed, the case ending fatally, a careful dissection of the uterus and uterine vessels after death may still reveal no macroscopic signs of disease. The diagnosis may turn almost entirely upon the results of blood-culture.

The presence of a bone injury in a child suffering from sudden fever must always receive the most critical examination; and the skeleton (especially the long bones) must be passed carefully under review if high fever, abrupt in origin, exists in a child without ascertained cause. Unfortunately, cases of infective osteomyelitis, due to *staphylococcus aureus*, become pyæmic so rapidly that even the early detection of the focus and its prompt treatment rarely serve to save the patient; but it is probable that some cases are saved by early recognition of their true nature, and some of them do not run this fulminating course. ***In all***

*instances where incisions are made into doubtful areas of inflammation cultures of the exuding fluid should be made, however innocent it appears to the naked eye.* Some surgeons are grave sinners in this matter. Now and again a drop of serum will yield a copious growth of staphylococci in the warm incubator within six to eight hours; this should at once lead to further surgical procedure if no fall has taken place in the temperature or in the leucocyte count, and if no alleviation has occurred in the general condition of the patient, as the result of the first incision (see p. 204).

4. *Malta fever*, unless the attention of the medical attendant is called to the possibility of this infection, may be the cause of fever of very obscure origin. Residence in a Malta fever district may have been of short duration, and no very obvious illness may have occurred whilst the patient was there. This was so in the case of a patient with very obscure fever, sent for investigation by Dr. Arthur Quennell, of Brentwood, and which proved to be a case of Malta fever. The patient may come under observation for the general weakness, for neuralgic joint pains, or for the fever, some months or even years afterwards, and may give no history suggesting the nature of his infection. The diagnosis is made either from a positive blood-culture (rarely possible in such a case), or from a combination of leucopœnia with agglutination of a strain of the causal micrococcus by the diluted serum of the patient. The habitat of the micro-organism in the delayed and prolonged cases of Malta fever is unknown. The most careful clinical examination may fail to demonstrate any possible focus (enlarged spleen, liver, &c.).

5. In *Malaria* the diagnosis rests upon the discovery of the parasite in the blood; a leucopœnia ('relative lymphocytosis') is almost invariable. A markedly intermittent

character of the fever, however, must never bias the observer unduly in favour of this diagnosis, even in the face of a clear history of ague in the past; for so many pyogenetic infections, local and general, are accompanied by this form of fever. The occurrence of rigors calls for the same caution. It may nowadays be taken for granted that if the patient has never lived out of England malaria is not the cause of his fever.

6. *Cerebro-spinal fever* is met with in its sporadic form with sufficient frequency to need consideration in connexion with fever of obscure origin. Occasionally there may be an absence of the diagnostic clinical signs for some days or even weeks: no stiffness of the neck or retraction of the head, no change in the 'reflexes' and, indeed, no signs of meningitis. A persistent headache, with pains in the back and limbs, and progressive loss of flesh—typhoid fever being excluded by a negative Widal and the presence of a leucocytosis—this state of things should lead to a lumbar puncture and a search for the meningococcus. The writer has known a young adult, suffering from this disease, to be treated for two or three weeks for rheumatic fever on account of the severity of his pains. In this case an intensely sour odour possessed by the sweat, which was profuse, added to the simulation of rheumatic fever.

7. *General tuberculosis* is, in the writer's experience, a rare cause of fever in patients who show no other physical signs of disease. From reading textbooks of medicine it would be inferred that the fact is otherwise, and that the physician has not infrequently to discriminate between this condition and such a disease as typhoid fever. Undoubtedly cases do arise in which generalized tuberculosis occurs (for some days up to two or three weeks) without evidence of focal lesions; but these appear to be very uncommon. The occasional

existence, however, of so desperate a state of things calls for great care in the diagnosis of any condition which may possibly be of this nature. Blood cultivated on ordinary media will not reveal the nature of the infection, and even if special media be used, the growth of the bacillus will be too slow in most instances to prove of any service. If the condition be suspected from the occurrence of a leucopœnia and the absence of agglutination reactions for the typhoid bacillus and the *Micrococcus melitensis*, films should be prepared direct from the blood and carefully stained by the carbol-fuchsin method. One or other of the tuberculin tests should be applied: the subcutaneous test is not available on account of the fever (see chapter xiii).

8. *Intestinal intoxication.* Under this heading there may be provisionally included a number of cases of fever which present no signs of a specific character, and ofttimes present no signs at all. No doubt the group contains cases having in reality wide differences in pathogeny. Relying upon individual experience of cases of obscure fever which have seemed to depend for their cause upon the absorption of poisons generated in the intestine, an attempt at segregation of these cases may be made, as follows :—

(i) In infants and in young children errors in diet, both quantitative and qualitative, are very commonly associated with fever. According to some well-known authorities, there is a variety of such troubles which deserves the epithet 'carbohydrate fever', this name being chosen because the kind of error in diet which underlies the condition is an excess of starchy stuff in the food. Examination of the stools in these cases shows them to be unduly pale, to be fermented and offensive. But excess of starch is, of course, by no means the only error which underlies the febrile dyspepsias of childhood. The prompt and good

effect of small doses of mercury and chalk, or of calomel, in many cases, suggests that excessive or unusual microbic action is a dominant feature.

(ii) The action of intestinal parasites contributes some of the cases. The fever may be due to direct absorption of the poisonous products of metabolism of the worm, aided possibly by the mechanical irritation set up by its presence and by its movements; or it may be due to poisoning of a secondary nature resulting from changes in the mucosa of the bowel. Thus, it seems certain that intestinal parasites cause colitis, often with the production of much mucus, which acts as a good nidus, not only for the parasite itself but for bacteria, such as streptococci and colon bacilli. A careful examination of the stools should be made in all cases of obscure fever, especially when occurring in children, not only for parasites but also for ova. One of the most mysterious and prolonged cases of recurring fever met with by the writer occurred in a girl in whose fæces, when they came to be examined, there were found to be enormous numbers of ova of Ascaris, with a good deal of mucus. This patient had been unsuccessfully vaccinated over a period of some months, with a colon bacillus isolated from the urine, under the impression that she was suffering from colon bacillus infection of the urinary tract. There were at no time, however, any urinary symptoms, and the stools had never been examined for parasites or other abnormality. During one of the bouts of fever, a dose of santonin, followed by vaccine prepared from the cultures obtained from the mucus in the stools, brought the illness to a rapid close, and the occasional exhibition of this drug with castor oil has since prevented any return of the fever.

(iii) Acute and subacute colitis. Physical signs may be confined entirely to the stools, which may contain mucus

in variable quantities, casts of the bowel, and occasionally blood.

(iv) In severe constipation it is not uncommon to see bouts of fever, and occasionally these are so marked that very natural doubts are entertained as to the presence of some focal inflammatory mischief (appendicitis, stercoral ulcer, pericolic suppuration) or of typhoid fever. There is always a leucocytosis present, which helps to exclude the last-named disease, but if the count is quite high local inflammation should always be suspected. In one case of this kind, a girl aged 18 years, who was under the care of Dr. Verling Brown at Sutton, the count reached 32,000. The pyrexia was also very high, reaching 105° on one occasion. The blood was found to be sterile on cultivation, and Widal's test negative. Neither Dr. Brown nor the writer could find evidence of any other condition than marked constipation, and this negative examination was confirmed by Sir Thomas Barlow and Mr. Mower White. But on the tenth day the illness terminated by the rupture of an abscess into the bowel and the passage of pus per anum. Such cases are always of a most anxious kind, for the fear that some more serious condition is present than intestinal auto-intoxication has constantly to be considered.

9. *Rat-bite fever.* The writer has recently had under his care at the Great Northern Hospital an unusual case of prolonged and periodic fever due to a rat bite. The man was originally attended by Dr. Hussey, of Farnham, who quickly recognized that there was something out of the ordinary about the patient's illness. The bite had healed very well, but about three weeks after it occurred the man fell ill with high fever, malaise, and an erythema of a curious kind, consisting of large, indurated, red plaques, about the face and limbs. All these things subsided, to be repeated after a quiescent period of three or four days. Dr. Hussey

then sent the man into hospital, where a similar state of things recurred five or six times, pyrexial periods of three or four days alternating with apyrexial periods of much the same duration. All kinds of investigations were made, but failed to discover any causal bacterium or hæmatozoan, either in the blood-stream or in the erythematous areas. The man eventually recovered without any specific treatment. During his stay in hospital it chanced that there was, under the care of Dr. Willcox and Sir Almroth Wright at St. Mary's Hospital, a very similar case. The writer has since had sent to him notes of three other cases of the same kind, in neither of which was it recognized that a specific disease was being dealt with. All these five cases recovered. In one of these last-mentioned cases a boy was bitten by a kitten, which had been seen to play with a dead rat immediately before the bite. There is, therefore, a disease having the following characters: The patient is bitten by a rat. After an incubation period of three to four weeks fever appears, accompanied by an erythema and much constitutional disturbance. A high leucocytosis is present. A quiescent period follows, during which the patient regains his normal state. The febrile bout recurs, and this alternation goes on for a variable time up to several months (in one of the cases it persisted for nearly eight months). Ultimate recovery takes place. No microbic or other cause has hitherto been discovered.

10. *Nervous fever.* Given that a thorough examination has been undertaken in a case of fever, and nothing has been discovered of the nature of physical signs, the question of nervous influence must be considered. Cases of nervous fever fall into two groups.

(i) Some persons 'run a temperature', as the phrase goes, more easily than others, just as some persons become

delirious with less provocation than others. Those people who possess an unstable thermotaxic mechanism cause much anxiety to their practitioners. And even when this peculiarity is known, the anxiety is not altogether allayed, for it must not be concluded without careful consideration that upon any particular occasion they are behaving differently from other patients. After an acute febrile illness the temperature of such persons, instead of settling down, is apt to remain irregularly raised, sometimes for several weeks, the patient meantime proceeding apace with his convalescence. These patients are generally very nervous people, and not infrequently there is something worse than mere neurosis in the family history. Much discretion is necessary in dealing with such a case. The practitioner stands to lose, whether the fever owns a definite organic cause or not: if he takes too little heed of the pyrexia, and events show that this has been significant of some important complication of the original illness, he is likely to be blamed for carelessness or ignorance; if he elaborates his investigations and the condition subsides without serious developments he is often blamed for unnecessary activity.

(ii) The second group of cases of nervous fever are of the nature of *Neuromimesis*. The neuromimetic patient is usually a young woman of a particular temperament, recognizable by the experienced clinician but very difficult to describe. Her morbid nervous state shows itself not only by pyrexia without organic cause, but also by the simulation of other pathological processes: anorexia, vomiting, skin eruptions and contractures. Cured, or rather cheated, of one of these, another takes its place. In nosology her disease belongs to that strange land which holds malingering at one pole and hysteria at the other;

her symptoms betoken less naughtiness than deserves the slur of the former epithet, and less system than to merit their being classed as the latter. In the younger patients precocity and 'being spoilt', and in those who are older a hopeless love-affair, are common ætiological factors. A careful study of the temperature curve may reveal suggestive features: the morning rise may be greater than the evening rise, and with the pyrexia there may be no associated increase in the frequency of the pulse and respiration. The patient, however, is not always of the type mentioned. The writer has seen prolonged and obscure pyrexia occur in a young married woman who had watched month after month the treatment of her phthisical husband in a sanatorium near by. During these weary months the routine of sanatorium life, with its temperature takings, its weighings, its dietings, and all its unavoidable daily reiterations, sufficed to bring about a state of nervous imitation of phthisis. She simulated her husband's disease very closely, for to the pyrexia she added considerable loss of flesh and a troublesome barking cough with hoarseness and occasional aphonia. She was rapidly and completely cured by six months' stay with convivial friends during the London season. So thin was she that physical examination of the chest was extremely easy; yet neither Dr. Holberton, her medical adviser, nor the writer could detect the slightest abnormality in the lungs or elsewhere. Mr. Frank Rose twice reported the larynx to be free from any evidence of disease.

To the foregoing causes of fever without other physical signs several others might easily be added; the individual practice of most observers will suggest cases which have taxed their acumen not a little. In this chapter the writer has only dealt with matters of personal experience.

# CHAPTER XVI

## TREATMENT BY SPECIFIC INOCULATION

*(The use of Bacterial Vaccines in Disease)*

### I. GENERAL

Bacterial vaccines have now become very generally recognized as valuable therapeutic agents in certain infective disease processes. This general recognition scarcely applies to continental cliniques, however—a state of things which is partly due to the fact that the inception of the vaccine treatment of pyogenetic diseases took place in England as the result of the labours of Sir A. E. Wright. That certain microbic diseases yield in a most satisfactory manner to the employment of specific vaccines is an established fact, and no practical account of clinical pathology can be regarded as complete if it does not deal with the methods of application of such treatment. The detailed steps in the preparation of vaccines will not be dealt with here, seeing that this lies outside the scope of most practitioners' work. To make the account of vaccine-therapy intelligible, however, a very brief reference will be made to the principles involved in such preparation. This reference is necessary because upon the practitioner often devolves the selection of the material from which is obtained the culture of the micro-organism used for the manufacture of the vaccine.

## II. THE PREPARATION OF THE VACCINE

By the term bacterial vaccine is meant a suspension of killed micro-organisms in some neutral liquid medium such as normal salt solution.

In preparing such a vaccine the object aimed at is so to treat the micro-organism that it may be obtained free from extra-cellular toxins, killed, and suspended in the salt solution for the purpose of subcutaneous injection. This suspension, or emulsion as it is usually called, is, to all intents and purposes, a preparation of the intracellular toxins of the micro-organism.

The first step is to isolate the causal micro-organism of the disease in pure culture. The method of doing this will depend upon whether the infection is local or general. (i) If a local lesion is to be dealt with, a portion of the exudate, secretion, or tissue concerned, is obtained, as free as possible from contaminations, and is forwarded promptly in a sealed sterile vessel to the pathologist. If the practitioner has culture tubes by him he may make his own cultivations and forward the inoculated tubes to the pathologist. In a few instances this is almost imperative; thus, in a case of pyorrhœa alveolaris, it is necessary to clean the surface of the gum thoroughly and to inoculate an agar slope with a little of the pus which is squeezed out from the pocket lying between the gum and the tooth (see p. 111). (ii) In the case of a patient suffering from a general blood infection without a local lesion, a blood-culture must first be made, care being taken that a sufficient quantity of blood is removed with appropriate technique (see chapter iii).

In most cases the infection is by a single micro-organism; sometimes, however, the infection is mixed, in which case a vaccine may be prepared from the various micro-organisms

separately. The bacteriologist will only prepare his vaccines from pure cultures. The colonies of growth are collected together, are scraped off the surface of the medium, and are transferred to a measured bulk of salt solution so as to form a uniform emulsion. This emulsion is then sterilized by being heated to 65° C. for an hour. The strength of the emulsion is estimated by actually counting the micro-organisms by the aid of a blood-counting apparatus. The vaccine is then diluted so as to yield appropriate doses per c.cm. and is transferred to small glass ampoules, which are sealed in the blowpipe flame. The greatest care is exercised, during this process of preparing the vaccine, to observe the principles of asepsis combined with accuracy.

## III. THE MODES OF ADMINISTRATION OF VACCINES

1. The common mode of administering vaccines is the *subcutaneous* one, and it is to this route that all subsequent remarks will apply. The method is extremely simple. The writer usually chooses the upper arm for the inoculation in patients who are not in bed. For those who are in bed, the region of the flank is generally chosen. There is, however, some reason for believing that the introduction of the vaccine near to the seat of a local lesion is occasionally of advantage. As to the exact depth to which the needle should be inserted to get a better result, whether into the subcutaneous tissue merely, or into the muscle, there is no knowledge to serve as a guide. Less discomfort seems to follow subcutaneous than intramuscular inoculation, and this fact may well determine the matter for the present. The skin is prepared by being rubbed with cotton-wool soaked in alcohol, or ether, or acetone. A small all-glass syringe and a clean sharp needle, which have just been boiled in water,

are used for the injection. The ampoule is well rolled between the hands to ensure uniform suspension of the bacteria, which may have formed a sediment due to standing. Some ampoules have rather wide necks; if they have it is advisable to tap the shoulder of the ampoule sharply several times in order to get the fluid in the neck below the file mark. The neck is then broken off and the contents are taken up into the syringe, care being taken to push out the air lying above the fluid prior to injection. As the bulk of fluid constituting the dose of vaccine is scarcely greater than many hypodermic injections in common use (vaccines are generally made up to 1 c.cm. = 17 minims), its introduction leads to no material discomfort to the patient. No dressing of any kind is necessary to cover the puncture.

2. The *intravenous* route has as yet been employed but little, and chiefly in an experimental fashion. No definite results have been recorded in connexion with the treatment of human beings by intravenous injection. In rabbits the writer has shown that the intravenous use of vaccines of appropriate size leads to marked immunization against infection by various pathogenic micro-organisms.

3. Upon the use of bacterial vaccines *by mouth*, again, very few observations have been made. Some authorities have administered tuberculin in this way, and recommend it. Considering the minute size of the dose which is usually employed, and the fact that its use subcutaneously is free from any inconvenience, it seems desirable at present to continue this latter method as tending more easily to accuracy of observations in regard to results. There is much need of carefully designed animal experimentation, not only in this but in several other moot questions connected with vaccine-therapy.

## IV. THE IMMEDIATE EFFECTS OF VACCINE INOCULATION

These immediate effects are local and general.

1. *Local effects.* There does not appear to be any uniformity of opinion as to how little or how much local 'reaction' should be aimed at when a vaccine is used therapeutically. When given for prophylaxis (e. g. *B. typhosus* vaccine against typhoid fever) a local reaction is anticipated. In the treatment of disease conditions, however, it is not certain that any definite reaction at the site of the inoculation is necessary in order to get good effects. It is probably correct to say that the degree of this reaction is directly proportional to the amount of the dose and also to the strength of the bacterial endotoxin. Unfortunately there is at present no standard of virulence of bacterial endotoxins. Different strains of the same micro-organism differ much in virulence, and a virulent strain is apt to lose its potency, it may be very quickly, on subculture. For these reasons it is a matter of great difficulty to anticipate the degree of reaction which a vaccine of known strength as regards the number of bacteria it contains will produce. The principle of practice with most workers, and with the writer, appears to be that in cases of chronic and of local infection a mild but definite reaction is aimed at, but in cases of acute and of general infection no reaction is sought. By a 'mild but definite' reaction is meant as follows: From four to eight hours after introduction of the vaccine a tender spot appears, surrounded by a small area over which the skin presents a faint blush. Slight swelling is also present, and this extends somewhat beyond the redness. The affected area is tender and there is slight stiffness of the

limb on movement. After eighteen to twenty-four hours the inflammation begins to subside, leaving only a tender spot, with slight thickening of the subcutaneous tissues. After forty-eight hours all these effects pass away. A dose which is unnecessarily large for its purpose, or which is very highly toxic, produces a more marked reaction, and may lead to redness and swelling of a large part of the arm and much attendant discomfort. It cannot be said that if no reaction at all occurs the dose used has been too small for its purpose. Care in the choice of the dose will almost always suffice to prevent an undue reaction; and this care should be exercised in every case, seeing that such extreme reactions rarely, if ever, appear to have any therapeutic benefit which may not be obtained without them. It happens quite often that such a moderate reaction as that just described follows the first of a series of doses of vaccines, but is not seen after subsequent doses, even when these are increased in size. After the injection of tuberculin (T.R.) in the therapeutic doses usually given nowadays no reaction at all is to be expected.

2. *General effects.* After the inoculation of a *prophylactic* dose of vaccine, when, as is the rule, a large dose is chosen, there is usually set up a fairly marked general disturbance: headache, lassitude, pain in the limbs, and a rise of temperature to 100°–102° F. These symptoms come on a few hours after the injection and subside during the second twelve hours. After the initial *therapeutic* dose in chronic infective processes nothing so severe as this occurs; but there is often a feeling of slight malaise during the day following the inoculation. In some cases the patient complains of nervous irritability, in others of drowsiness. After the initial dose, even if the number of micro-organisms be increased, it is unusual to see any such general effects. With the small

doses chosen in the treatment of acute and generalized infective processes no constitutional disturbance supervenes. In chronic and local infective processes, even if there be slight initial disturbance, this is often followed by a state of general invigoration, in some cases quite marked.

## V. THE PROPHYLACTIC USE OF VACCINES

In preventive medicine the principle of inoculation has been applied on a large scale to *plague*, to *typhoid fever*, and to *cholera*. In each of these diseases a certain amount of active immunity appears to be conferred by specific inoculation, and various methods of carrying out the principle are still on trial. Of late years a good many animal experiments have been made relative to the prophylactic use of vaccines, but much still needs to be done in this direction. The susceptibility of rabbits to infection by staphylococci and streptococci may readily be lessened by inoculation with moderate doses of vaccines prepared from these micro-organisms. This raises the important question whether a similar result may not be brought about in patients who are to be submitted to operations involving risk of pyogenetic infections afterwards, as in removal of the tongue, &c. Such protective vaccination has, indeed, been introduced into surgery and is actually practised by a few careful surgeons. The inoculations should be made during the week but one preceding the operation. It is not uncommon for patients who have recently been inoculated on account of furunculosis or some other staphylococcal infection, to remark upon an unwonted freedom from suppuration when they incur some accidental damage to the skin or deeper tissues. It has been shown experimentally that rabbits enjoy a very high degree of

immunity to the endotoxin of the meningococcus after prophylactic inoculation by killed cocci, and it is possible that children might with benefit be inoculated in a similar manner in the presence of an epidemic of *cerebro-spinal meningitis*. Such inoculation has been proved by Dr. Mervyn Gordon and the writer to be harmless when applied to human beings.

1. The chief use in England of prophylactic inoculation by killed bacteria is in connexion with *typhoid fever*. Persons going into districts abroad where typhoid fever is endemic, especially if they are adolescent, and therefore at a susceptible age, are well advised to be thus inoculated. There is a growing mass of evidence that such vaccination confers a relative immunity which may last for several years. The inoculation should be made at least one week before the person sails, so that the resulting malaise shall not increase any tendency there may be to seasickness. In order to lessen both the malaise and the local reaction at the site of inoculation, it is advisable to give the vaccine in two doses with a week's interval. The writer's own practice is to inject a dose of 1,000 million killed typhoid bacilli and to follow this after an interval of seven or ten days by a second dose of 2,000 million bacilli. The vaccine is freshly prepared, and two or three different strains of typhoid bacilli are used in its manufacture. The first dose is conveniently given at such a time that the person inoculated can arrange to stay indoors and have little or nothing to do during the next day. The extent of the reaction differs considerably in different individuals; it is not usually sufficient to make lying in bed a necessity. It has generally passed off forty-eight hours afterwards. The second dose, though of double the size, usually produces a much slighter reaction than the first; this second dose may therefore be given as late

as the day before embarking, or, if the patient be a good sailor and the voyage is to last longer than ten days, this dose may be given on board. It should be remembered, however, that it is desirable to allow a clear fortnight to elapse between the inoculation of the second dose and the time of arrival at the district where typhoid fever is rife. This is not the place to enter into a consideration of statistics relating to the value of prophylactic inoculation. Suffice it to say that evidence appears to be accumulating in favour of such practice in regard to typhoid fever.

2. Reference has already been made to the prophylactic use of *colon bacillus* vaccine prior to surgical operations upon regions already infected by this micro-organism. The writer has upon several occasions used similar vaccine in a prophylactic manner in cases of chronic bacilluria and chronic cystitis and prostatitis, in which it has appeared to him quite impossible to get rid of the micro-organisms from the urine by therapeutic vaccination. Despite assertions to the contrary, experience shows that a condition of bacilluria is not amenable to vaccine-therapy. And in cases of chronic cystitis and pyelitis, in which constitutional and local symptoms are absent, and in which the sole knowledge of anything being wrong turns upon the discovery of micro-organisms in the urine, it is very doubtful if a sterile urine ever results from vaccine treatment. But in all these cases it is probable that a series of doses of appropriate vaccine is of service in preventing those exacerbations of the morbid state which constitute a ' flare up ', recognizable alike to practitioner and patient. It is also probable that by the same means a spread of the infection to other parts of the urinary tract and to the kidneys is in great measure prevented.

3. The use of *tuberculin inoculation* is indicated over a prolonged course of time as a prophylactic measure in patients whose pulmonary or other lesions have become 'quiescent' or 'arrested' by other modes of treatment, whether carried out in conjunction with therapeutic inoculations or not. Upon the return to ordinary life, for example, of a phthisical patient who has undergone sanatorium treatment with satisfactory results, a course of inoculation may well be added to those non-specific measures which, if he be wise, the patient has learnt to weave into his daily routine (see p. 136).

4. Even in dealing with the less serious microbic infections which are so eminently amenable to vaccine-therapy, such as *furunculosis* and *pustular acne*, it is advisable to make assurance doubly sure by increasing resistance in a prophylactic manner some time after the disease has been cured. This statement holds especially for acne, in which a tendency to recurrence will almost certainly exist if the patient has not yet arrived at the age which provides natural immunity to this trouble. In the early days of inoculation a pardonable enthusiasm led to extravagant promises in regard to the permanency of cures wrought by this means. Experience, and the readiness with which patients whose ailment has to do with the complexion give expression to their disappointment, have damped much, though not all, of this enthusiasm. The practitioner will do well to insist upon an occasional prophylactic dose of mixed staphylococcus vaccine in all such cases.

5. Quite recently attempts have been made to immunize persons against certain acute microbic infective processes of a different class by means of inoculation. The infective processes referred to are *influenza, acute rhinitis and naso-pharyngitis* ('common cold'), and various forms of *acute sore*

*throat.* Although it is much too early to draw any conclusions regarding the results of such prophylactic treatment, a few comments of a general kind may not be out of place in regard to it.

When faced with the question as to the practicability of protective inoculation against *influenza*, the first consideration which arises is whether or not the causal microbe of uncomplicated influenza has as yet been isolated. Despite the claims made in this respect for Pfeiffer's bacillus, there remain several points lacking in the complete proof that this micro-organism is the *materies morbi* of the disease. It is quite possible that Pfeiffer's bacillus is but the most frequent of the various secondary infective agents common in the disease, and that the essential causal factor in the primary infection is unknown. If this be so a close analogy exists in respect of certain ætiological points between influenza and scarlet fever. For just as in scarlet fever the uncomplicated disease is usually a somewhat trivial affair, its common association with pathogenic streptococci rendering it ofttimes very serious, so in influenza a sharp but short febrile attack, of itself not often very troublesome, may become of grave import when complicated by other infections. In addition to Pfeiffer's bacillus, the *pneumococcus* and *M. catarrhalis* are perhaps the most common micro-organisms found in association with influenza.

It follows from this argument that when a person is 'immunized against influenza' by inoculation with *B. influenzæ* there is a large presumption underlying the treatment, and he would indeed be a bold physician who promised a successful issue to his venture. But such experiment, if carried out on a large scale upon susceptible persons, would be very valuable. It appears to be the custom of some 'immunizators' to inoculate 'against

influenza ' by a mixture of vaccines derived from Pfeiffer's bacillus, *pneumococcus* and *M. catarrhalis*, a frank confession of doubt as to the specificity of the first-named microbe. The procedure, however, seems rational, seeing that, as already stated, the ill effects of the disease are in great measure due to the secondary infections that are commonly grafted upon it. An alternative to this triple-barrelled measure is to await an attack in the susceptible person and to investigate the flora of the upper respiratory tract during the first twenty-four hours of the disease. Actual information is thus yielded concerning the nature of the infective process, and a vaccine, which has the great advantage of being autogenous, may be prepared for present and for future use. In a few cases in which, after a fair statement as to the experimental nature of the whole process, patients have desired the writer to attempt a process of protective immunization in this way, the results have been very promising. But it is worthy of note that as often as not the micro-organism against which these patients have been vaccinated has been another than Pfeiffer's bacillus, e. g. *pneumococcus*, *M. catarrhalis*, and a strain of *streptococcus*.

The present position of prophylactic inoculation in regard to *colds* is much the same as it is in regard to influenza. The writer's own practice is to await an attack, to obtain an expert quantitative estimation of the flora of the nasal mucus early in the course of the illness and to proceed accordingly. Several times it has happened, in doing this, that the dominant micro-organism has been quite another than might have been anticipated. Here again a prevalent practice, but in the writer's opinion a bad one, is to inoculate with a vaccine prepared from a mixture of several micro-organisms commonly found in acute nasal catarrh.

The writer has had experience of prophylactic inoculation

in several cases of recurring *acute sore throat*, in most instances streptococcal in nature, and can report some very satisfactory results. In these cases the preparation of an autogenous vaccine is imperative, for the streptococci at work vary much in different cases.

## VI. CASES SUITABLE FOR TREATMENT BY BACTERIAL VACCINES

At the present stage of our knowledge of specific inoculation as a therapeutic measure, still very largely an experimental stage, it is impossible to lay down any definite rules that will guide the practitioner in his choice of cases likely to give good results. Assuming that he does not share the obsession, held by a few authorities on the subject, that vaccine-therapy is a panacea for all diseases that are of microbic origin, the reader will perhaps not deem it without value if the results of the writer's experience, which has been fairly extensive, are here set before him, rather than a restatement of the conclusions of others. Too little distinction has been made, in the opinion of the writer, between certain hypotheses connected with the mode of action of bacterial vaccines and the ascertained facts of actual observation. And seeing that as yet little or no experimental work has been done along the lines of curative vaccine-therapy, the only way by which the hypotheses can be properly tested is the individual experience of various workers.

Scarcely any infective process exists, whether local or general, chronic or acute, of known micro-biology, which has not been dealt with by way of specific inoculation. Like all new forms of treatment, the scope of the method is at present being enlarged to its utmost. When the disappointments have been properly noted and the successes temperately recorded, some proportionate view of the usefulness of this

system of treatment will doubtless be revealed. In the meanwhile no curb need be put upon any reasonable trial of the method; rather should every opportunity be taken of testing its efficacy. The only desiderata are careful technique and an unbiased review of results. As in the employment of other modes of treatment, so here: much room exists for accurate observation, but none for enthusiasm.

Following the plan already suggested of stating the facts of individual experience, a few comments will now be made concerning various infective disease-processes that have appeared to the writer to be amenable to treatment by specific inoculation. For this purpose infective processes may be considered as—

*A.* Local infections { (*a*) chronic. (*b*) acute.

*B.* General infections { (*a*) chronic. (*b*) acute.

## *A.* (*a*) CHRONIC LOCAL INFECTIONS

Up to the present time this group of diseases has probably yielded the best results to vaccine-therapy. The diseases that have been dealt with are discussed below, under the headings of the micro-organisms most often producing them.

1. *Staphylococci.* Chronic local infections which are most often due to this micro-organism are *boils*, *carbuncle*, *sycosis*, *pustular acne*, some forms of *eczema*, *ciliary blepharitis*, *otitis media*, and *suppurating meibomian cyst.* Of these diseases boils react best to the treatment; so well do they react that a cure, more or less long-standing (see p. 180), may confidently be promised to almost every patient. Historically the first of the staphylococcal infections to be treated by Wright's method, furunculosis still remains the most responsive to the new therapeutic measure. Taken as a whole

the furunculosis group of cases stands almost alone in respect of the uniformity of results obtained with the treatment. So much so that a guarded prognosis must always be given in the other forms of staphylococcal infection. But even here individual cases often do remarkably well, though now and again they are disappointing. In acne some degree of success may always be promised, but the ultimate result differs according to the various ætiological factors present. As an adjunct to other modes of treatment vaccine-therapy is invaluable. If attention to the general health, digestion, &c., be omitted, and no pains be taken with the toilet of the skin, failures will certainly be met with in those cases where the infective element is not dominant. Patients are ofttimes too sanguine on account of the glowing testimonial of some friend whose lesions were quite different from their own; they must be led to modify their expectations, and must be prepared to add to the inoculation treatment the less novel aids to recovery already referred to.

Under the same heading may be mentioned the treatment of *sinuses* left after the bursting or opening of abscesses, or after operations. Here it is of great importance to commence treatment early. It goes without saying that efficient surgical measures must always be undertaken in conjunction with the inoculation treatment; to overlook an abscess or to neglect proper drainage of a sinus is but to court disappointment. Vaccine-therapy is often an adjunct, but never a substitute, in sound surgery.

2. *Streptococci and pneumococci.* Chronic local infections by these micro-organisms are less common. *Pyorrhœa alveolaris* is, in the opinion of the writer, always due to *Streptococcus salivarius*, and some cases of the disease respond well to vaccine treatment. *Suppuration in the nasal sinuses*

*and middle ear*, of streptococcal or pneumococcal origin, sometimes responds favourably, though here again obvious measures for effective drainage must be attended to.

3. *Gonococci. Chronic urethritis* often responds well to vaccine treatment, but care must be taken to identify the micro-organisms present in individual cases. Secondary invasion of the urethra by staphylococci (especially) is common in chronic gonorrhœa, requiring the use of staphylococcal vaccines. In cases of *gleet* which fail to respond to local treatment a course of gonococcal vaccine should always be tried. That form of gonorrhœa which shows recurrences of the discharge after quiescent periods, often of some duration, seems to react favourably to inoculation.

4. *Bacillus coli. Infections of the urinary tract* are those most often submitted to this form of treatment. The results are not, in the view of the writer, so uniformly good as is commonly held by many authorities. Individual cases vary much, as well in their chronicity as in the extent of the damage already done in the bladder and pelvis of the kidney. It may be definitely asserted that in those cases in which symptoms are present, such as frequent micturition, local discomfort, pyrexia, anæmia, loss of weight, &c., considerable or complete alleviation may be expected to follow the treatment. The amount of pus present in the urine often becomes much less or it disappears. Contrary to what is often stated, however, a state of colon bacilluria is usually unaffected by vaccine treatment (see p. 179). *Chronic otitis media* due to this micro-organism sometimes responds well, as also do cases in which *sinuses* are primarily or secondarily infected. The *post-operative suppuration* not infrequently seen in cases of *appendix abscess* is a condition pre-eminently amenable to vaccine-therapy, and some of the most successful instances of treatment by specific inocula-

tion are found in this class of surgery. Delayed convalescence after appendicectomy should always raise the question of chronic infection of deep-seated tissues, and thorough examination of the patient and of the sinus (if one be present) should be made with a view to vaccine treatment. The most striking instance seen by the writer of response to vaccines in a case of this kind occurred in the case of a young man under the care of Dr. Wreford, of Hampstead. As the case illustrates several of the points seen in this condition it may serve as a good example of the application of vaccine-therapy to this class of case. Mr. Gask removed a gangrenous appendix forty-eight hours after the commencement of a fulminating attack of appendicitis. At the time of the operation there was noted to be considerable local peritonitis. The temperature fell a few hours after the operation, but the patient began to lose flesh rapidly, and suffered from periodic bouts of exhausting diarrhœa and occasional vomiting. Two tubes inserted anteriorly and posteriorly for purposes of drainage remained almost dry, and there was complete absence of any effort at healing in the wounds. A month after the operation, when the patient was seen in consultation, emaciation was so marked that it was with difficulty that the skin was kept whole over the anterior parts of the iliac crests. No signs of reaction to the poisoning were present, the temperature was subnormal, the pulse infrequent, there was scarcely any leucocytosis (7,000), the edges of the wounds were indolent, and there was no pus exuding from either of the tubes. A blood-culture proved to be sterile. A diagnosis of chronic local peritonitis was made. A little dark-brown grumous material obtained from the bottom of one of the sinuses grew on cultivation *B. coli* and *Staphylococcus aureus* in about equal numbers. A mixed

vaccine was prepared and so measured as to contain 5,000,000 of each micro-organism per c.c. A dose was given twenty-four hours after the patient had been seen. The effect was both prompt and satisfactory. The temperature and pulse-rate rose, pus appeared from the tubes, and the wounds became more healthy in appearance. A second dose of the same size was given on the third day and a third dose of double the size on the sixth day. Progress was uninterrupted from the time the vaccine treatment was begun; the patient was able to get up fourteen days after the first inoculation. Only six doses were given altogether. A specimen of pus examined after the third dose grew *staphylococcus albus* only; the second three doses of vaccine were therefore prepared from this micro-organism.

5. *B. typhosus.* Suppurating foci which are sequels to *typhoid fever* are favourable for vaccine treatment. Dr. Andrewes has recently treated a very intractable case of periostitis due to this micro-organism with excellent results.

6. *B. tuberculosis.* The treatment of chronic tuberculous infections by inoculation is considered in chapter xiii.

### *A.* (*b*) ACUTE LOCAL INFECTIONS

Under this heading come a larger number of cases of streptococcal origin, and fewer cases due to staphylococci.

1. *Streptococci.* In *erysipelas* recovery seems to be frequently hastened by one or two small doses of streptococcus vaccine. The nature of the streptococcus is, of course, *S. pyogenes*, and care must be taken that the vaccine used is made from this particular strain. It is better, too, that it should be made from a strain of *S. pyogenes* which has caused erysipelas. If it is possible to cultivate the micro-organisms from a vesicle of the actual case under consideration, so much the better. Early administration

is very important, especially in infants, for the disease may undermine the patient's resistance before the response to the vaccine can take place. It must constantly be borne in mind that vaccine-therapy depends for its results upon a mechanism of *active* immunity, and active immunity presupposes a modicum of effective vitality. Promptness is therefore an important consideration in the examination of any available material and in the preparation of the vaccine. Both these processes are sometimes possible within the course of twenty-four hours, for it often happens that a pure culture of *S. pyogenes* is obtained from a vesicle on the spreading margin of the erysipelatous area of skin, and from this culture vaccine can be at once directly prepared.

In *cellulitis* also the dominant microbe is usually a streptococcus. Here, and in *acute abscess* due to the same infection, inoculation may hasten healing after proper surgical measures have been undertaken. So also in *empyema sinus* (often pneumococcal) and other forms of post-operative suppuration.

2. *Staphylococci. Acute boils* and *carbuncles* tend to abort when treated with an early dose of vaccine, and no ill effects appear to follow such treatment. In favour of treating these conditions by vaccine is the fact that either of them may prove more serious than at first sight promises. Thus, subsequent unfavourable developments may be due to the position of the lesion, e. g. near to the inner canthus of the eye, leading to orbital abscess or even to meningitis, or they may be due to the general condition of the patient, e. g. the enfeebled resistance of old age. For these reasons any opportunity of influencing the patient's degree of immunity beneficially by vaccine treatment at an early stage should certainly be undertaken. If it appears probable that a boil or a carbuncle, when first seen in the stage of redness and induration, will eventually 'come to a head',

this sequence may be encouraged by the use of a large dose of vaccine, i. e. 1,000 million cocci. In this way time may be saved and eventual scarring may be minimized. In the case of boils of the external auditory meatus, of the nose and of other situations which are very painful, such saving of time is much appreciated by the patient.

### *B.* (*a*) CHRONIC GENERAL INFECTIONS

These cases are more limited in number. In chronic *gonococcal arthritis* very good results quite commonly follow the use of vaccines. Localized stiffness and pain in the feet, even when of several years' duration and having resisted all other forms of treatment, will sometimes respond very definitely to inoculation. The writer has had one case of gonococcal spondylitis, chronic in nature, recovering after vaccine treatment. In chronic *staphylococcal pyæmia* inoculation should be tried, but the results do not seem to be very pronounced, especially when the lesions are in connexion with the bones. In *chronic infective endocarditis*, whether the micro-organism be a streptococcus (as is generally the case), Pfeiffer's bacillus, pneumococcus or staphylococcus, the treatment by vaccines, though occasionally attended by encouraging results for a time, probably never saves the patient ultimately. The writer has arrived at this conclusion after very considerable experience of these cases. Yet so futile are all other modes of dealing with this distressing disease that a good trial of specific inoculation should always be made. Early diagnosis is probably essential to the success of the method, and seeing that a blood-culture is positive in the great majority of the cases before as yet the patient shows signs of severe constitutional deterioration, this method of examination becomes imperative (see chapter iii).

### *B.* (*b*) ACUTE GENERAL INFECTIONS

As yet the employment of bacterial vaccines in the treatment of this group of diseases has been of a very tentative kind. Moreover, it is very difficult to estimate the effects of such treatment. Seeing that in most cases of general infection 'auto-inoculation' is proceeding apace, good results from the method would not be anticipated. But various observers have nevertheless attempted cautious inoculation of such patients from time to time, the hypothesist because he has sometimes found the opsonic index to be low and the empiricist because he has been anxious to ascertain the effective range of this system of therapeutics. It is quite certain that the results have been much less promising than in cases of localized infection. It would appear that the more acute and generalized the infection, the less marked are the benefits of specific inoculation.

In *pneumonia*, where the natural course of the disease gives a good criterion by which to judge of the effect of any form of specific treatment, the crisis does not appear to be hastened by the employment of pneumococcus vaccine. As a matter of routine, however, the writer is in the habit of giving one or two small doses of vaccine to all cases which are not running a favourable course. It is unlikely that any definite information will be forthcoming on the matter until a large series of cases has been treated by the help of vaccines, so that a comparison can be made between the mortality of this and another series not so treated, the two series being concurrent as regards season and place.

*Puerperal fever, osteomyelitis, acute infective endocarditis*—these and other forms of acute generalized infection are diseases of such a serious nature, and end fatally with such frequency, that the tentative use of appropriate vaccines

is quite justifiable, provided all the other known aids to recovery are employed. The results at present obtained, however, are very discouraging. Since the introduction of specific inoculation in the treatment of pyogenetic infections, antisera seem largely to have fallen into disrepute, probably undeservedly so. The writer believes the combination of both methods of treatment to be eminently rational and not seldom to prove beneficial. Immediately the diagnosis of acute streptococcal or pneumococcal infection is made, whether generalized or local, a full dose of antiserum should be given, preferably beneath the skin; this should be repeated after twelve hours. Meantime efforts should be made to isolate the infecting agent, from which a vaccine may be prepared for use in small doses in conjunction with further doses of serum.

In *typhoid fever* the writer's experience of vaccine treatment is too limited to draw conclusions. In one very severe case, in which marked 'meningism' was present, and in which the micro-organism was cultivated from the cerebro-spinal fluid as well as from the blood and from the urine, the use of small doses of autogenous vaccine appeared to produce decidedly beneficial results, which were followed by a good recovery. In another case, under the care of Dr. J. H. Jennings, two doses of ten million killed bacilli, given on the twenty-eighth and thirty-first days of the illness, appeared to produce marked improvement in the symptoms and were followed by rapid defervescence. It seems desirable to exhibit the vaccine in any protracted case of the disease.

A prolonged case of *Malta fever*, transferred to the writer's care by Dr. Arthur Quennell, of Brentwood, certainly seemed to respond very favourably to vaccine treatment.

# CHAPTER XVII

## TREATMENT BY SPECIFIC INOCULATION

*(Continued)*

### VII. THE CHOICE, AND THE FREQUENCY OF ADMINISTRATION, OF THE DOSE OF VACCINE

BEFORE entering upon a detailed account of dosage of bacterial vaccines in various diseases, it is well to make the frank admission that the writer takes experience as being the chief guide in the matter. Fallacious as this guide is notoriously known to be, he considers it more useful than the guide which is said to control the inoculations of many who make a study of this mode of treatment of infective processes; that is, the opsonic index. There are numerous reasons for considering that the opsonic index, though it may be of some value in diagnosis, does not always measure the degree of total immunity of a patient to the infecting micro-organism. These reasons cannot well be gone into here. Whether it is that this opinion has come to be shared by a growing number of clinical pathologists, whether the hypothesis upon which the opsonic index rests is now regarded as more improbable than was the case formerly, or whether, as is more likely, a determination of the opsonic index has been found to be unnecessary for the purposes of actual practice, need not be dwelt upon. It is quite certain that a very large amount of highly successful specific inoculation goes on to-day which is quite uncontrolled by opsonic determinations. It is equally certain that these empirical inoculations are very

frequently undertaken by workers who formerly taught that such proceedings were highly dangerous and were to be strongly deprecated. But if opsonic estimations were necessary once they are necessary now. It is worthy of note that wholesale chemists are provided with stocks of vaccines to be retailed to the medical profession, and the vaccines are advertised as being made by the very authorities who, a short time ago, insisted upon the necessity of the opsonic index as a control of the treatment. In the chemists' advertisements there are instructions for the use of the vaccines, which assure the practitioner of the safety of the remedies, even when empirically administered. These same instructions specify the size of dose to be used in various diseases, irrespective of opsonic determinations. It seems an obvious inference from these facts that the early position taken up by the 'opsonists' is no longer tenable.

For the choice of dose and for the frequency of its administration reliance should be placed upon a careful study of the clinical condition of the patient and upon experience of similar cases already treated. There is good evidence from animal experiments, as the writer has shown, that the effective range of dosage of bacterial vaccines is fairly wide, and that within this range no ill effects are likely to ensue to the patient. An equal degree of immunity to staphylococcal infection may be conferred upon rabbits by the use of vaccines differing in amount in similar animals by as much as 100 per cent. It may also be shown that animals will tolerate very large doses of bacterial vaccines when injected subcutaneously, without loss of weight and without other evidence of ill health. Of greater importance than these observations on animals is the fact that in man the careful employment of vaccines, uncontrolled by opsonic

indices, has not led to any of those dire calamities which were predicted for it. On the other hand, it has led to a large number of good results in the treatment of bacterial infections, and promises still better results when experience of the treatment shall have ripened.

In the initial stage of this form of therapeutics, beyond which the physician has not yet passed, it is not surprising that great differences of opinion and of practice exist in regard to dosage. It does not, however, follow that even when experience of the treatment is much greater than at present the question of dosage will settle down into one fixed rule which all will observe. Despite the many observations that have been made with regard to the use of anti-diphtheritic serum, opinions still vary as to the optimum size and frequency of dose; but the results of this therapeutic measure are, in the main, universally good. And in this instance, be it observed, there is no existing hypothesis which claims to control the question of dosage. It is not only in matters of specific serum and vaccine-therapy that discordant opinions in regard to dosage are found. It is now many years since potassium iodide became universally recognized as the proper drug to exhibit in a certain stage of syphilis; an enormous amount of experience of its action has accumulated, yet one practitioner prescribes it in three-grain doses and another in thirty, and both record equally good effects. The doses of vaccine suggested below are those which are generally employed by the writer. They are set out tentatively, for they are by no means arbitrary, being modified in individual cases as seems necessary.

One of the great difficulties attending the question of dosage of bacterial vaccines is the *variation in virulence* of different strains of the same micro-organism, and of the same strain after subculture. Particularly does this

difficulty apply to various strains of the *streptococcus* group, to the *pneumococcus*, and to the *gonococcus*. It is very doubtful if this difficulty is sufficiently recognized by those authorities who claim that the opsonic index gives a correct guide to the amount of vaccine (bacterial endotoxin) which should be employed. Tables of suggested doses, say of killed gonococci, which are recommended by an observer for use in particular cases, lose much of their value on account of this important fallacy. Experience shows that whereas in the case of one strain a dose of five million killed gonococci produces a marked local reaction at the site of inoculation, and is followed by an exacerbation of a urethral discharge, in the case of another strain neither of these effects follows the use of a dose of a hundred million killed cocci. Another difficulty in the adjustment of dosage, though apparently a less disturbing factor than that just named, arises from the individual differences seen in the response made by various patients to the same dose of the same strain of a micro-organism. This difference is often seen in the simple case of prophylactic inoculation against typhoid fever. Three persons may be inoculated with the same 'stock' vaccine at the same time; one will show very little local or general reaction, another will present a moderate degree of both, the third will suffer from a red, swollen, and painful arm, with considerable malaise and pyrexia. If in the three persons the curve of the opsonic index shows the same characters, which it may do, it is concluded by some that the same degree of the immunizing process has occurred in each. But in the face of the differing degree of response as judged by clinical observations, this conclusion cannot be accepted without some criticism. A similar position exists, in a more complicated fashion, in regard to many cases of curative inoculation.

1. *Prophylactic dosage.* Reference has already been made to the dosage usually employed in preventive inoculation against *typhoid fever* (see p. 178). In *plague* prophylaxis, when this method is employed, the vaccine is prepared from a four weeks' old broth-culture of the bacillus. The culture is sterilized by heat and 3 c.c. of it are inoculated subcutaneously as a single dose (Haffkine). In *cholera* prophylaxis the same worker employs, for the first dose, 1 c.c. of vaccine prepared from an attenuated culture, and for the second, after a few days' interval, 1 c.c. of vaccine prepared from a more virulent culture.

In prophylaxis against *pyogenetic infections* during, or after, surgical operations, a large dose of vaccine, appropriate to the particular infection feared, is used. Thus, a dose of 1,000 million killed staphylococci, or killed *B. coli*, is injected ten days before the operation. When the operation is to be performed upon an organ or region of the body which is already infected, the methods set out under the heading of curative dosage should be resorted to.

Before undertaking a research connected with certain virulent strains of meningococci, Dr. Mervyn Gordon and the writer were both inoculated with a dose of vaccine estimated at two hundred million killed cocci. The result in each case was a definite local reaction, slight leucocytosis, and slight malaise. This may therefore be regarded as a safe prophylactic dose for any person desiring immunization against *cerebro-spinal fever* by this method.

2. *Curative dosage.* It follows from remarks already made that in the writer's opinion no definite rules can be laid down for the size of the dose of vaccine which it is desirable to use in the treatment of various infective processes. The following principle may, however, be safely stated; *the more virulent the micro-organism, and the more acute and the more*

*generalized the disease process, the smaller should be the dose of vaccine employed.*

In the following suggestions for dosage infections will be considered in the order already observed when discussing their suitability for vaccine treatment.

### *A.* (*a*) CHRONIC LOCAL INFECTIONS

1. *Staphylococci.* Cases of *furunculosis* are those which most often call for treatment. Custom with regard to dosage has changed at least twice since the introduction of vaccine treatment for this condition, and this despite the fact that the principles underlying the opsonic hypothesis have not altered. It is probable that the changes have been the natural result of clinical observations, oscillations such as often occur in medical opinions pending the trial of a new remedy. At first comparatively large doses of cocci were used, at least 1,000 million, and this dose was often increased still further. Some of the results proving unsatisfactory, the pendulum swung in the other direction, and doses of 100–250 millions were considered appropriate initial doses. Some workers still use such doses, but most observers agree that 1,000 millions is the best dose with which to begin the treatment of an ordinary case. This is followed by doses of 250–500 millions, with intervals of seven to ten days, if improvement follows the first dose. Should relapses occur, it is probably either because the dose is not high enough, or because inoculations are too frequently repeated, and this can usually be discovered by a little care. Much individual difference exists in this matter. In most cases the doses of vaccine can be 'spaced' further after the fourth dose, allowing fortnightly, three-weekly, monthly, and two-monthly intervals. It must be confessed that by proceeding

in the opposite manner, and graduating the doses upwards, equally good results are as often obtained. Thus, 250 millions may be given as the initial dose, 500 millions a week later, and 1,000 millions at the third or fourth inoculation. This latter method is perhaps better for patients who are constitutionally affected (e.g. diabetics, &c.). *Chronic carbuncle* is treated in the same way, whether surgical interference be also adopted or not. In the treatment of *acne* much the same line is adopted. In nearly all cases the concurrent use of local applications will be found of advantage. The exact relation of Sabouraud's bacillus to the lesions of acne is still a matter of debate. Dr. Alexander Fleming has recorded good results from the use of a mixed vaccine of staphylococcus and the 'acne bacillus'. In *sycosis* the response to the smaller doses used in furunculosis is usually good if the treatment is carried out early. If, however, the case is of some standing, and deep-seated inflammation with induration is present, the effect of the inoculations is not so good. In such long-standing cases good effects will sometimes follow dosage of 2,000–5,000 million cocci when previous inoculation by smaller doses produces very little result. The same remark applies to some cases of long-standing acne with much induration. In connexion with sycosis, as with acne, it is courting disappointment to neglect other forms of treatment, such as epilation and the free use of mercurial applications. In *chronic sinus infections*, again, the result of small doses of vaccine is usually disappointing; these sinuses are apt to be lined by fibrous tissue, and they need radical surgical treatment, with vaccines as an adjuvant. In *ciliary blepharitis* success usually follows the use of doses recommended for furunculosis.

2. *Streptococci and pneumococci.* In chronic infections

by these microbes smaller doses of vaccine are to be used than in cases of chronic staphylococcal infection. In *pyorrhœa alveolaris* it is advisable to commence with doses of 10 million cocci, increasing this gradually, at intervals of 8–10 days, if necessary to 100–200 millions. If unsatisfactory response be obtained, even these latter doses may be increased. In chronic pneumococcal infections it seems rarely necessary to use doses of more than 50–75 million cocci; thus, in *empyema sinus*, a series of weekly doses may be given, commencing with 10 millions and increasing gradually to the above figure.

3. *Gonococci.* There appears to be more difference of opinion as to the choice of dose in the use of gonococcal vaccine for chronic infections than in the case of any other micro-organism. Reference has already been made to the great variations in virulence of different strains of gonococci, and no doubt the difference of opinion is largely due to this fact. In the treatment of *chronic urethritis* and of *gleet*, some authorities recommend doses as small as 10–15 millions, others as large as 100–200 millions. The writer's practice is to commence with a small dose (10 millions) to test the patient's degree of response, and to increase the dose gradually until results are obtained. Whilst the dose is still small, it may be given at intervals of 3–4 days; when doses of 100–200 million are reached, the interval should be 10–14 days. It must be remembered, however, that these figures apply to a vaccine of known virulence. In the writer's experience every new gonococcal vaccine is of doubtful virulence until it is tested, and therefore no fixed rules can possibly be laid down for the size of dose of any particular one. It is a question whether the gonococcal vaccines sold by chemists are, for this reason, of any service at all, unless the practitioner is prepared to neglect the

advertised dosage and make trials on his own account. It is certain that, though the terms of the advertisement remain the same, the vaccine sold with it does not. *Gonococcal iritis* requires great care in the choice of dose of vaccine; very small doses probably suffice. In one recurring case of this disease, under the care of Mr. William Lang, and inoculated by the writer, an initial dose of 10 million cocci, given during a quiescent period, caused considerable activity in the eye, followed, however, by a more satisfactory resolution than had occurred upon former occasions. After waiting for another period of quiescence, a dose of 5 millions produced a similar, though less marked, result. This patient was evidently very susceptible to the gonococcus endotoxin, and this was borne out by the fact that a few hours after the initial dose was given the metacarpo-phalangeal joint of the right index-finger became swollen and slightly painful. This joint had been affected after the original urethral infection more than ten years before, a fact which the patient had quite forgotten when questioned concerning the occurrence of joint troubles. This event shows that gonococcal vaccine may act in a gonorrhœal patient as old tuberculin acts in a tuberculous patient—it may lead to a specific 'reaction'. It may even be used as a test, therefore, for the presence of active gonococcus infection.

4. *B. coli.* In cases of chronic *colon bacillus cystitis and pyelocystitis* the initial dose of vaccine may be 20 million bacilli, followed, at weekly intervals, by doses gradually increasing to 50, 100, and 200 millions; it is a good plan to spread the treatment over a period of two or three months. The writer makes a practice of cultivating the urine every three or four weeks, and if the progress is not satisfactory, a fresh batch of vaccine is made up from the most recent

culture. If no improvement follows the above-named doses, they should be increased to 500 or even to 1,000 million bacilli. Other forms of chronic infection by this bacillus may be treated after the same manner.

5. *B. tuberculosis.* Dosage of vaccine against chronic infection by this micro-organism is discussed in chapter xiii.

6. *Actinomycosis.* In a case of infection due to this microbe, reported as cured by inoculation, the dose used was $\frac{1}{1000}$ mgr. of the growth obtained on solid medium, administered weekly for a period of six weeks.

## *A.* (*b*) ACUTE LOCAL INFECTIONS

It is even less practicable to frame rules for dosage of vaccines in acute cases of infection than it is in chronic cases. Close attention to the individual case, the extent and the intensity of the local reaction, the degree of the general resistance as indicated by amount of strength, condition of pulse, &c., the temperature curve, the leucocyte count from day to day—these alone serve to guide the practitioner in his choice of the size and the frequency of the dose. The question whether vaccine treatment should, or should not, be tried in these cases, has already been dealt with (see p. 188). If, after careful consideration of the whole condition, it is decided to administer vaccines, these should be given in very small doses, and the effects should be carefully watched.

1. *Streptococci.* In *erysipelas* and in *streptococcal cellulitis* an initial dose of 2½ or 5 million killed cocci may be given. Reference has already been made to the desirability of working with a vaccine freshly prepared from the case under treatment. If improvement appears to follow, the dose may be repeated on the third day, and again after a similar

interval. Or, if the improvement be certain, a somewhat larger dose may be given on the second occasion.

2. *Staphylococci.* Acute staphylococcal infections, such as *acute boils and carbuncles*, and '*poisoned fingers*' of staphylococcal origin, are treated by doses of 20–50 million killed cocci, and the response is usually satisfactory. After *acute abscesses* have been dealt with surgically, healing is considerably hastened by the use of similar doses, repeated, and, if necessary, gradually increased, every third or fourth day.

3. *Gonococci.* In the great majority of cases of *gonorrhœa* inoculations are not indicated, the response to local and general treatment of the customary kind being satisfactory.

4. *B. coli.* Acute colon bacillus infections often respond very well to one or two doses of 10–20 million killed bacilli.

### *B.* (*a*) CHRONIC GENERAL INFECTIONS

1. In chronic *staphylococcal pyœmia*, the most helpful method of procedure is to administer 50–100 killed cocci every 4–7 days, omitting the inoculation just prior to, and just after, any surgical treatment of abscesses or sinuses that may develop.

2. In chronic *streptococcal pyœmia* the doses should be smaller; 10–20 million cocci, given in similar fashion. In one such case, following scarlet fever, the writer has seen good effects follow three weekly doses of 25, 50, and 50 million cocci respectively.

In *chronic infective endocarditis*, the initial dose should be 10 million killed micro-organisms (streptococci, pneumococci, *B. influenzæ*, &c.), repeated every 4–7 days. If no good effect follows these doses, they should be increased to 20, 30, or 50 million cocci, the temperature chart, leucocyte curve, &c., being carefully studied meanwhile.

3. In *chronic general gonococcal infection*, treatment should be commenced tentatively with doses of 10–20 millions to test the virulence of the strain of coccus used (see p. 200). The dose will probably need a considerable increase before good effects follow—to 50, 100, and 200 million cocci. Cases of gonococcal arthritis vary so much in their degree of chronicity that no practical help can be given by any statement of a general kind. The writer has, upon two or three occasions, failed to get any response until doses of 400–500 million cocci have been tried. Some American 'immunizators' have given as much as 1,000 million cocci for a single dose, and have reported satisfactory results therefrom.

## *B.* (*b*) ACUTE GENERAL INFECTIONS

The question of the advisability of using vaccines in cases of *acute septicæmia* has been dealt with elsewhere (see p. 191). Even when it is decided to use them the dosage must necessarily be of but a tentative kind, the treatment being tried warily in each individual case. All those clinical observations referred to under acute local infections must be made daily (p. 202), and must be taken as guides to the employment of the vaccine. Three illustrative cases are appended; in all of them recovery occurred concurrently with the use of specific inoculation.

CASE 1. *Osteomyelitis of ilium; staphylococcus aureus pyæmia.*—The patient was a man aged 35 years. *S. aureus* was isolated in pure culture from the local lesion and from the blood-stream. The abscess in the bone was opened without any abatement of the symptoms; a few days later an abscess was also opened in the shoulder-joint. The patient was extremely ill, and his life was despaired of. A dose of 50 million killed cocci, prepared from the positive

blood-culture, was administered, and this was quickly followed by marked improvement. A similar dose was given five days later. Four days after this second dose the dose was increased to 100 million cocci; the condition still further improved, and the temperature now became normal. Ten days after this third inoculation pus was withdrawn from a knee-joint; *this pus was sterile on culture, and the knee-joint did not require further drainage.* A fourth dose, consisting of 100 million cocci, was now given. The patient recovered completely, his sinuses healing rapidly. He was discharged from hospital quite well, three months after admission.

CASE 2. *Operation for removal of tonsils and adenoids; streptococcal septicæmia.*—The patient was a boy aged 4 years. Ten days after the operation he was found to be ill, and to have a temperature of 102°. The presence of chronic otitis media suggested the possibility of meningitis, but two lumbar punctures at intervals of three days gave normal cerebro-spinal fluid on each occasion. On the twentieth day after the operation, the illness having continued, a blood-culture yielded a pure growth of *Streptococcus pyogenes.* A dose of vaccine consisting of 5 million killed cocci was given, followed by two subsequent doses of 5 and 10 million cocci respectively, at intervals of four days. A second blood-culture, after the third dose of vaccine, was sterile. The boy made a rapid recovery.

CASE 3. *Operation for acute otitis media; streptococcal septicæmia.*—The patient was a woman aged 25 years. The operation was followed by a rapid rise in temperature and symptoms of a severe general infection. Cultivations from the wound and from the blood both yielded a pure growth of *S. pyogenes.* Pending the preparation of the vaccine, the patient was given normal horse-serum by the

mouth, and this was continued daily during the period of treatment by inoculations. Five million cocci were given as the initial dose, followed by two more doses of the same size on alternate days, and a fourth dose of 10 million cocci. A blood-culture now undertaken proved sterile. The patient's improvement commenced immediately after the inoculations were begun; recovery was complete.

Following the experience of such cases as the above, the writer advocates treating acute septicæmia by very small doses of the killed micro-organism obtained from the patient, repeated every third or fourth day, e.g. 5 million streptococci or 10 million staphylococci. It may even be preferable to give still smaller doses and to inoculate daily, but of this mode of dosage the writer has as yet made no extended trial.

### VIII. THE USE OF STOCK VACCINES

Several of the stringent rules originally laid down for the employment of vaccine-therapy have lately been relaxed, as well by those authorities who enunciated such rules as by those who from the first doubted the wisdom of proceeding by rule at all in a path as yet so little trodden. One of the first of these rules to yield was that which made it imperative to employ a vaccine made from the micro-organism actually isolated from the patient under treatment. It has become a moot question whether this particular rule has not been relaxed too much, and whether the indiscriminate use of vaccines that are kept in stock by the wholesale chemists will not shortly bring the whole subject of vaccine-therapy into disrepute. For the 'stocking' of vaccines leads to a temptation to waive the important matter of bacteriological diagnosis, without which successful treatment cannot possibly be expected. Moreover, it is certain that vaccines

deteriorate by keeping; whenever it is possible, therefore, the particular vaccine used should be specially prepared for each patient. There are instances, however, in which the use of a stock vaccine is not only allowable but compulsory. Thus, it may be advisable to treat gonorrhœal arthritis in a patient from whose blood, joints, and urethra no gonococci can be isolated; in this case appropriate doses of a vaccine recently prepared from another strain, or, better, from a number of different strains, are therefore given. Again, in a case of erysipelas it may not be possible to cultivate the streptococcus which is most probably the cause of the skin infection; a small dose of *Streptococcus pyogenes* vaccine obtained from another case of erysipelas, or, failing this, from any case of acute *Streptococcus pyogenes* infection, is administered. But such procedures should always be regarded as 'second best', and are to be strictly reserved for cases of the kind mentioned. There is a second group of cases of bacterial infection in which it is customary to employ 'stock vaccines'—that in which the cultivation of the micro-organism concerned is very difficult and its growth very slow. Examples are all cases of tuberculosis, and some of actinomycosis and other streptothrix infections. Commercial tuberculin, in the form of T.R., is almost invariably used in the vaccine treatment of tuberculosis. But even here it should be remembered that vaccine specially prepared from the patient's own strain of tubercle bacillus may conceivably lead to a better result. And recent methods of facilitating the growth of the bacillus on artificial media render this procedure less difficult than formerly. Lastly, it is sound practice to use a stock vaccine of a more virulent strain of micro-organism than the one isolated, or of a mixture of several different strains, if it is found that little or no good follows the use of the micro-

organism actually present in the lesion treated. Reference has already been made to the good effects sometimes seen to follow the use of vaccine prepared from virulent strains of *Staphylococcus aureus* in such infections as pustular acne, usually due to *Staphylococcus albus*. Similarly, it is occasionally found that vaccine made from a strain of *B. coli* isolated from a case of acute peritonitis produces good results in a case of chronic colon bacillus cystitis, in which vaccine of the autogenous kind produces little effect.

## IX. CONCLUSION

That this account of vaccine-therapy is of a somewhat sketchy and inconclusive nature follows from the fact that present knowledge of the subject owns the same defect. The matter has been purposely dealt with only in the light of the writer's own experience, because any advance in knowledge must come from the recording of facts rather than from the reiteration of hypotheses. Although the writer is convinced that vaccine-therapy constitutes an instrument of very great utility in stimulating the natural defensive mechanism of the body against many forms of microbic infection, he considers that much has still to be learnt in regard to the most effective methods of using that instrument. It may be that no more effective methods than those indicated in this account will be forthcoming until knowledge of the processes of natural immunity is more complete than it is at present.

Vaccine-therapy is not to be regarded as a panacea for all diseases which are of microbic origin. Still less is it to be regarded as a panacea for all diseases. It is a valuable adjunct in the medical and surgical treatment of bacterial infections.

# INDEX

* *Note*: The earlier numbers refer to the choice of cases; the later numbers refer to the choice of doses.

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